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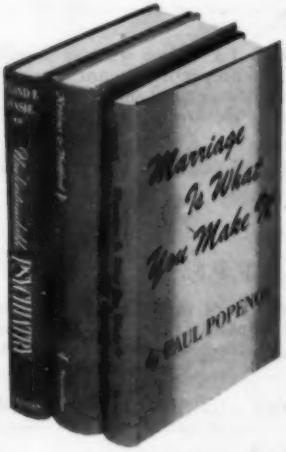

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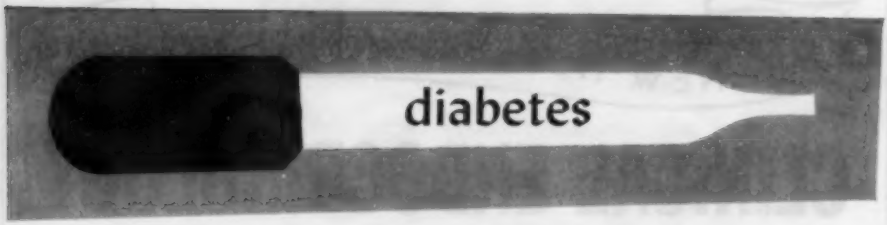

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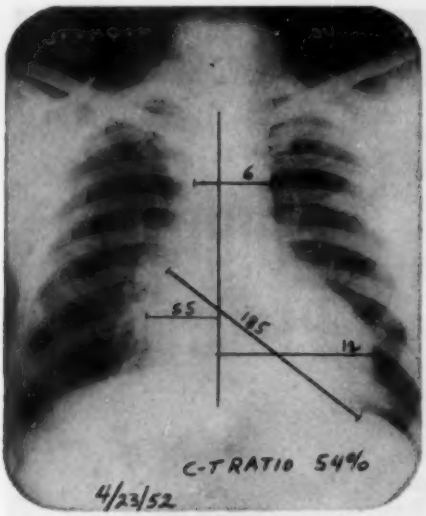

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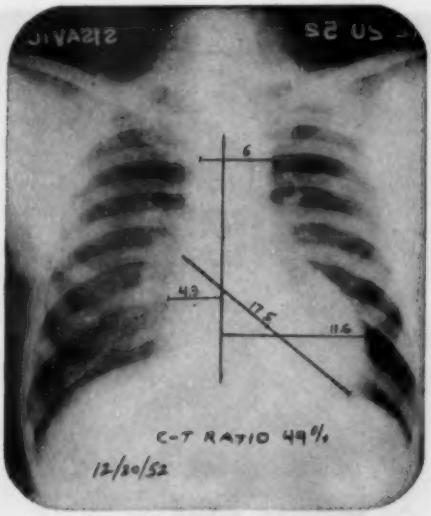

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1. Kuhn, P. H.: Angiology *4*:195 (June) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: Am. J. M. Sc. *225*:379 (April) 1953.
3. Moyer, J. H.; Miller, S. I., and Ford, R. V.: J.A.M.A. *152*:1121 (July 18) 1953.

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2. Humphreys, P., *et al.*: Angiology *3*:1 (Feb.) 1952.
3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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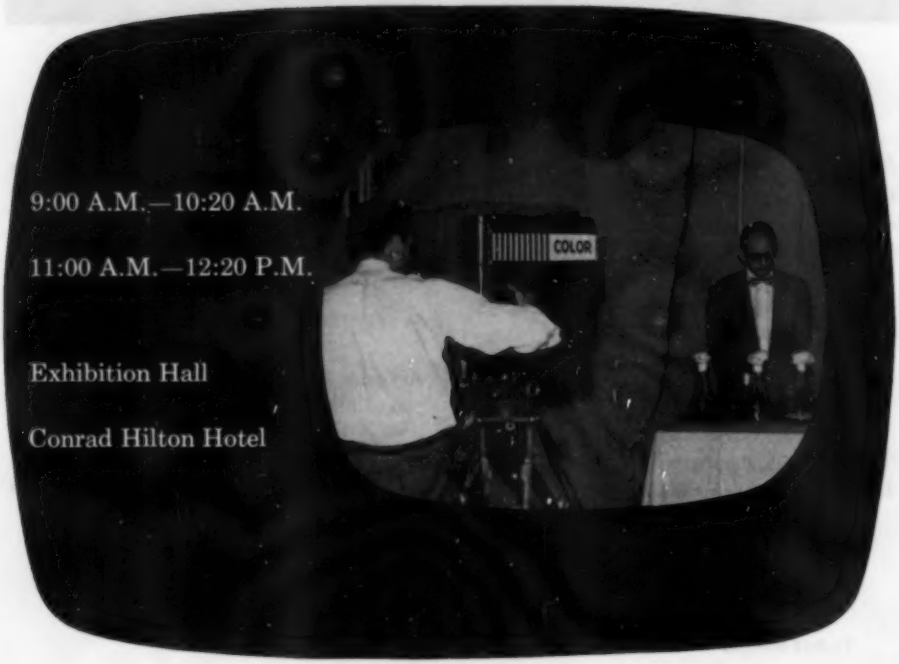

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2. Rohn, R. J., and Bond, W. H.: Journal-Lancet *73*:317 (1953).
3. Berk, W., et al.: New England J. M. *240*:754 (May) 1949.
4. Berlin, N. I.: J. Biol. Chem. *187*:41 (1950).

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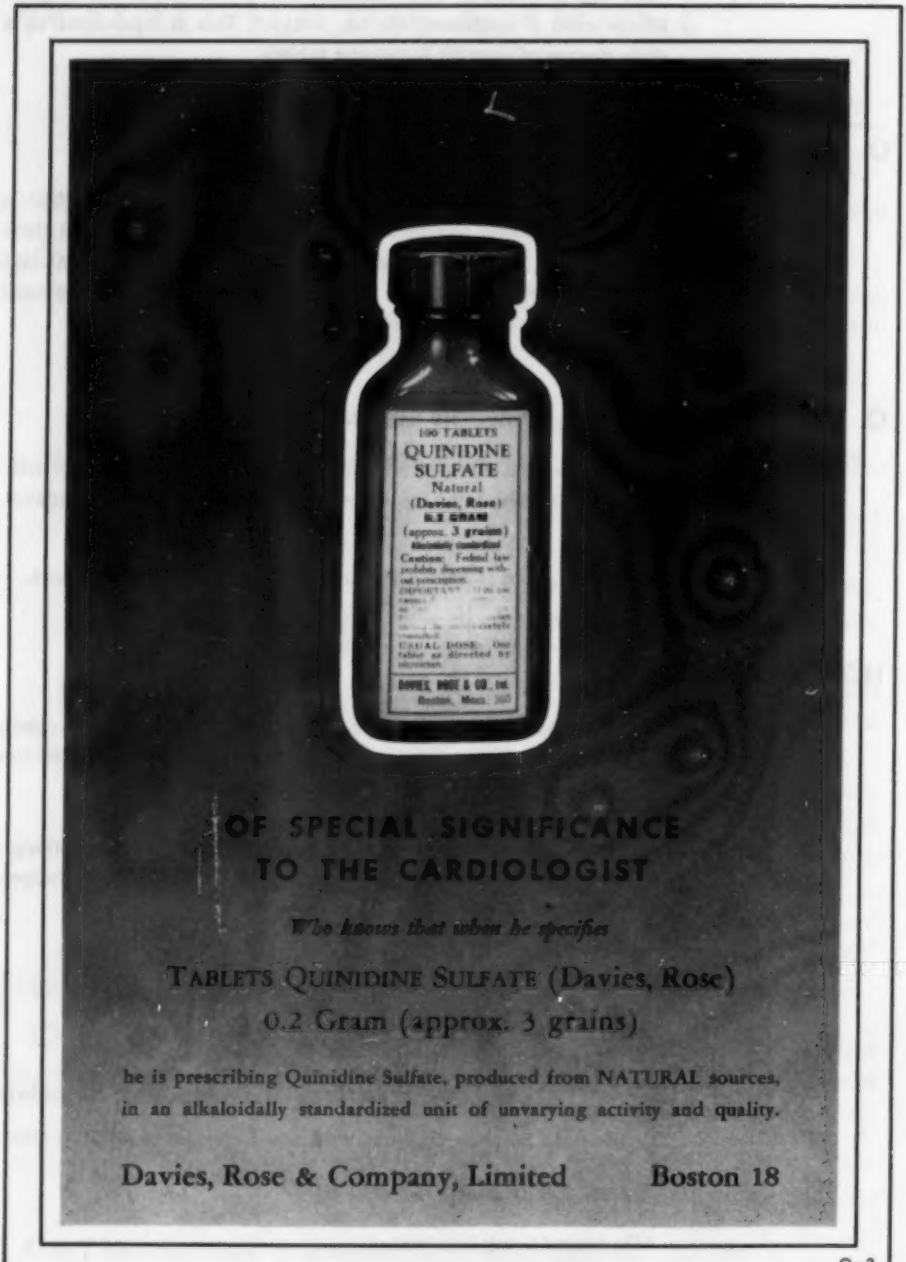
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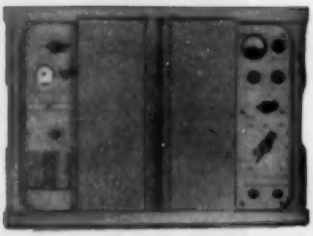

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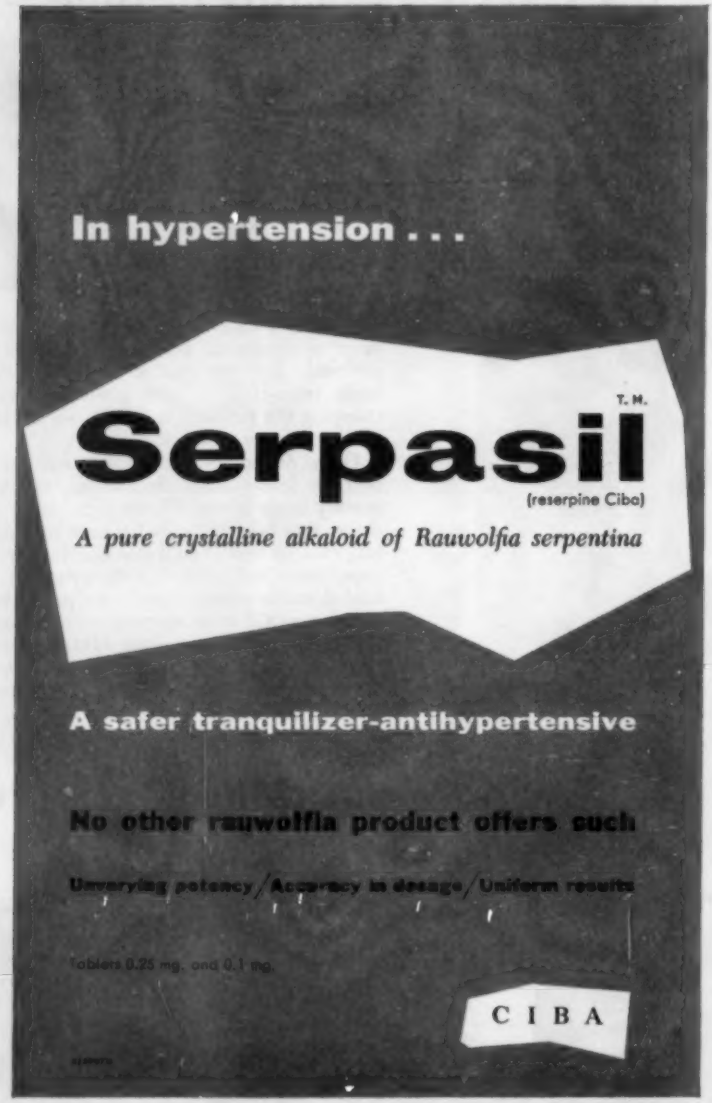
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'Spansule' 'Spansule' 'Spansule' 'Spansule' 'Spansule' 'Spansule' 'Spansule'

IN ECLAMPSIA **UNITENSEN®**

Brand of Cryptenamine (Irwin, Neisler)

the first and only isolated Veratrum alkaloid preparation with an unparalleled safety ratio of →

Unitensen provides **CRYPTENAMINE**, the first—and only—isolated Veratrum alkaloid preparation which does not induce vomiting on the same (or approximate) dose as that which exerts hypotensive action.

INDICATIONS

Eclampsia, preeclampsia, and preeclampsia with underlying essential hypertension.

Available at present as a parenteral preparation, containing 2 mg. per cc. (260 C.S.R.* Units) of cryptenamine, in 5 cc. multiple dose vials.

*Carotid Sinus Reflex

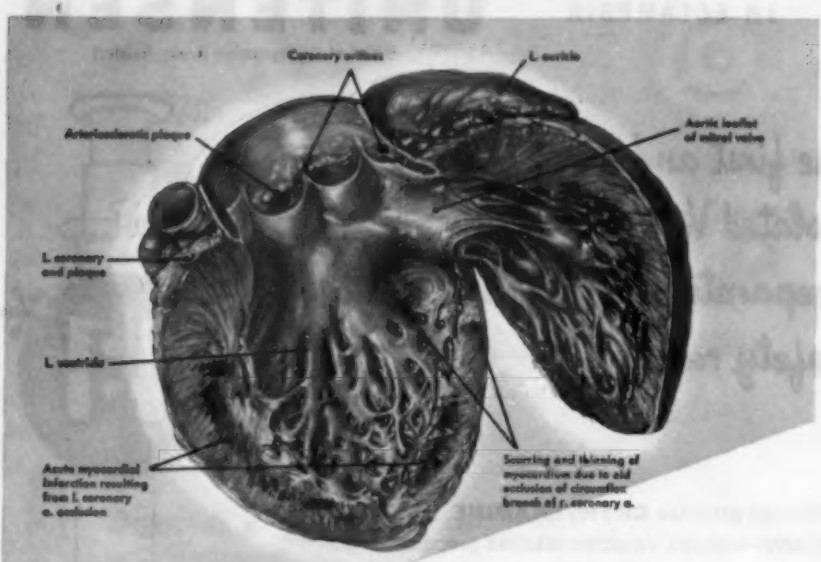
*Assayed Biologically**

Information concerning technique of administration and abstract on request.

Comparison of Unitensen with Protoveratrine and three other alkaloid preparations

DRUG	EMETIC : THERAPEUTIC RATIO	THERAPEUTIC INDEX
UNITENSEN (cryptenamine, Irwin-Neisler)	**4:1**	125
Protoveratrine A & B	1:1	20
Commercial Alkaloid Preparation A	1.2:1	40
Commercial Alkaloid Preparation B	1:1	—
Commercial Alkaloid Preparation C	1:1	—

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS


Coronary orifices
L. auricle
Arteriosclerotic plaque
Aortic leaflet of mitral valve
L. coronary and plaque
L. ventricle
Acute myocardial infarction resulting from l. coronary a. occlusion
Scarring and thinning of myocardium due to old occlusion of circumflex branch of l. coronary a.

Myocardial Infarction with Severe Shock:

Reduction of Mortality

"... in correcting the state of shock we have enabled certain patients to recover from the initial episode, which otherwise gave every indication of culminating in death."[1]

Levophed infusion causes a striking rise in oxygen tension in areas of myocardial ischemia produced by coronary obstruction.[2] "It is therefore reasonable to suppose that the restoration of arterial pressure to a level consistent with an adequate coronary flow must limit the size of the infarct, save healthy myocardium, shorten the period of shock, and lessen the likelihood of congestive failure at a later date."[3]

"Severe cardiogenic shock demands therapy... the most efficacious method of treatment now available is use of vasopressor drugs."[4] "Current usage favors nor-epinephrine."[5]

References:

1. Kurland, G. S., and Molnar, Martin: *New England Jour. Med.*, 247:383, Sept. 11, 1952.
2. Sayen, J. J., et al.: *Jour. Clin. Investigation*, 31:658, June, 1952.
3. Gilchrist, A. R.: *Brit. Med. Jour.*, 2:351, Aug. 16, 1952.
4. Miller, A. J., et al.: *J.A.M.A.*, 152:1198, July 25, 1953.
5. Levine, H. D., and Levine, S. A.: *Med. Clin. North America*, 37:935, July, 1953.

WINTHROP-STEARNS INC.
New York 18, N. Y. • Windsor, Ont.

WINTHROP

Levophed®
BITARTRATE
Brand of Levarterenol bitartrate (nor-epinephrine)
THE MOST POWERFUL PRESSOR ANTIDOTE FOR
Shock

Supplied: Levophed bitartrate solution 0.2 per cent (equivalent to 0.1 per cent base), ampuls of 4 cc., boxes of 10. (Each 4 cc. to be administered in 1000 cc. of 5 per cent dextrose.)

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Methamphetamine Hydrochloride, COMPRESSED

Subtle improvement in mood and outlook follows oral administration of small doses of 'Methedrine'. This helps carry depressed patients through their troubles, toward normal adjustment.

For those whose troubles stem from eating too much, 'Methedrine' makes all the difference between continual self-denial with consequent irritability, and easy acceptance of a reducing diet; it dispels excessive desire for food.

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'Methedrine' brand Methamphetamine Hydrochloride, 5 mg., Compressed, scored

Bottles of 100 and 1,000

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ACHROMYCIN*

Hydrochloride Tetracycline HCl *Lederle*

ACHROMYCIN is a new and notable broad-spectrum antibiotic.

Several investigators have reported definitely fewer side reactions with ACHROMYCIN.

ACHROMYCIN maintains effective potency for a full 24 hours in solution. It provides more rapid diffusion in tissues and body fluids.

On the basis of clinical investigations to date, ACHROMYCIN is indicated in the treatment of beta hemolytic streptococcic infections, *E. coli* infections, meningococcic, staphylococcic, pneumococcic and gonococcal infections, acute bronchitis and bronchiolitis, and certain mixed infections.

CAPSULES { 250 mg. / 100 mg. / 50 mg.

INTRAVENOUS { 500 mg. / 250 mg. / 100 mg.

SPERSOIDS* Dispersible Powder { 50 mg. per teaspoonful (3.0 Gm.)

Other dosage forms will become available as rapidly as research permits.

*Reg. U.S. Pat. Off.

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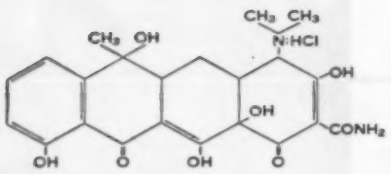
FEWER SIDE EFFECTS



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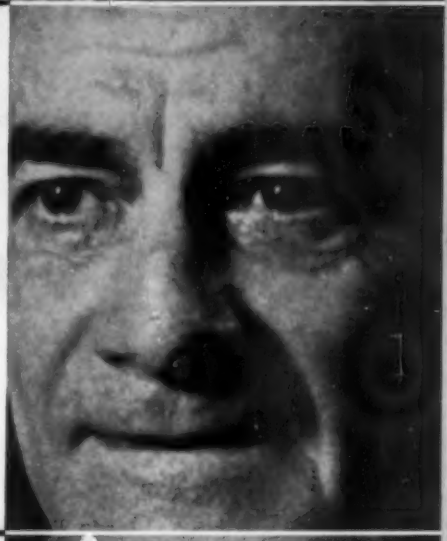
'Dexamyl' helped

...a "confused" old lady

...an extremely nervous man



..."a typical alcoholic"

(Photographs and excerpts of case histories from the files of a general practitioner.)

Patient S. M. (80) was "plagued with nervousness, profound weakness, vertigo, and pain . . . add to this the untimely catastrophic death of a daughter."

'Dexamyl', initially 4 tablets, then 2 tablets daily, relieved "her nervous uncertainty, her depressive weariness, her melancholia, and her tearfulness . . . also her vertigo. . . . 'Dexamyl' helped her to smile again."

Patient L. H. (51) "had positive tremors of the eyelids, tongue, fingers, lips and voice. . . . His complaints always centered about extreme nervousness, jitteriness, depression, and 'all-gone weakness'.

" 'Dexamyl' allayed inward tension . . . gave him a sensation of amelioration and comfort. . . . Yet, even in this intensely irritable patient, there were no side effects [from dosages] as high as 2 tablets every 3 hours on several attacks. . . .

"He is now able to work and support himself, which he was unable to do for several years."

Patient T. H. (62), although basically a fine individual, had become "a typical alcoholic".

"His emotional balance became seriously disturbed and he would cry and exhibit depressive characteristics, with or without intoxication.

" 'Dexamyl', 2 to 4 tablets daily, decreased his demand for liquor and gave him an increased sense of well-being. Emotional balance was more easily sustained; daily habits more normal. . . . Sleep, for the first time in years, was more tranquil."

Dexamyl*

tablets and elixir

—relieves both anxiety and depression

—promotes a feeling of composure

Each tablet provides the synergistic action of two mood-ameliorating components: Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital, ½ gr. (32 mg.). Each teaspoonful (5 cc.) of the elixir is equivalent to one tablet.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

FOR RAPID AND
SUSTAINED RELIEF IN

bronchial asthma

HP*ACTHAR *Gel* meets the practical requirements for successful treatment of bronchial asthma in the patient's home and the physician's office. The need for hospitalization is greatly reduced, even in severe cases.

HP*ACTHAR *Gel* acts rapidly—essential in the acute paroxysms of asthma. Therapeutic action is sustained over prolonged periods of time, resulting in a diminished need for injections: One or two per week suffice in many instances.

HP*ACTHAR *Gel* can be a life-saving measure in status asthmaticus. Remissions up to 18 months duration have been reported.

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HP* ACTHAR® *Gel* is The Armour Laboratories Brand of Purified Adrenocorticotropic Hormone—Corticotropin (ACTH).

Subcutaneously
or intramuscularly as desired
with Minimum Discomfort
Home and Office Treatment
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Significant Economy

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Keeps patients on hexamethonium therapy comfortable

URECHOLINE®

Chloride

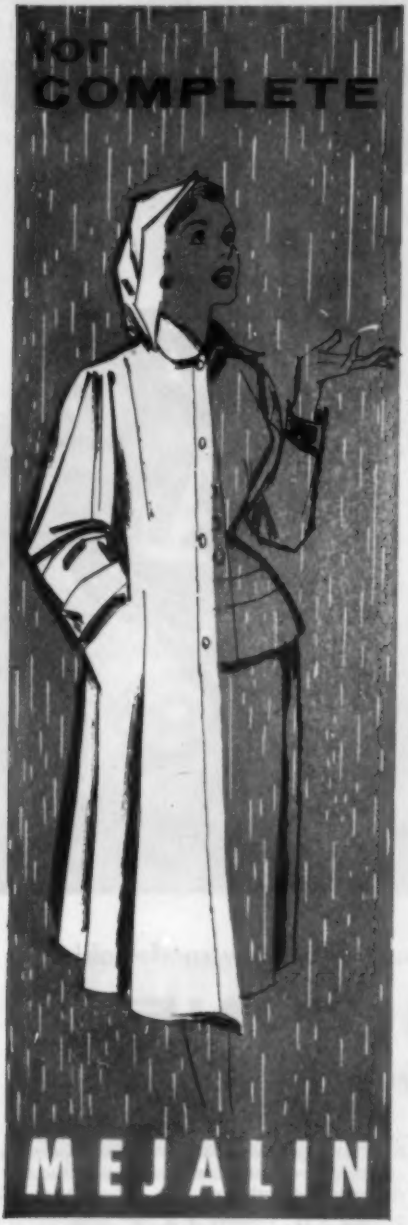
(BETHANECHOL CHLORIDE, MERCK)

ACTION: Hexamethonium therapy produces parasympathetic as well as sympathetic blockade. The former is reflected in the hypertensive patient as side effects including nausea, constipation, and paralytic ileus. URECHOLINE has been reported to be the most satisfactory parasympathomimetic agent[1] for overcoming undesirable and sometimes grave side-effects. This drug is also most valuable for urinary retention, another hexamethonium-induced side-effect. Its use increases patient cooperation and permits the continued administration of hexamethonium compounds. URECHOLINE is valuable given either to *prevent* the appearance of advanced hexamethonium-induced side-effects or to *control* such disturbances.

1. Freis, E.D., Finnerty, F.A., Jr., Schnaper, H.W., and Johnson, R.L.: *Circulation* 5:20, Jan. 1952.

SUPPLIED: 5-mg. tablets, bottles of 100; 1-cc. ampuls containing 5-mg. each of URECHOLINE Chloride.

COUNCIL ACCEPTED



PROTECTION you need a WHOLE RAINCOAT

for complete B complex protection

MEJALIN—and only MEJALIN—supplies all 11 identified B vitamins plus liver and iron

B complex protection may be needed by that overworked executive with "no time to eat" . . . by that balky youngster that turns up his nose at mealtime . . . by your elderly patient who doesn't like the right foods—in fact, by anyone who eats poorly or sporadically or who requires an extra measure of vitamin support.

Since "vitamins, especially those of the B complex, are closely interrelated" and "lack of availability of any one may affect the metabolism of the others,"[1] the importance of a complete B vitamin product is apparent.

Mejalin provides all the identified B vitamins plus liver and iron as an extra safeguard for good nutrition.

Two exceptionally pleasant dosage forms assure patient acceptance.

1. Therapeutic Nutrition, Publication 234, National Research Council, 1952.

One teaspoon of Mejalin Liquid or one Mejalin Capsule supplies:

Thiamine	1 mg.
Riboflavin	1 mg.
Niacinamide	10 mg.
Pyridoxine hydrochloride	0.2 mg.
Pantothenic acid	1 mg.
Choline	50 mg.
Inositol	20 mg.
Vitamin B_{12} (crystalline)	3 mcg.
Folic acid	0.2 mg.
Biotin	0.02 mg.
Para-aminobenzoic acid	0.5 mg.
Liver fraction	300 mg.
Iron (from ferrous sulfate)	7.5 mg.

Mejalin Liquid contains panthenol and soluble liver fraction N. F.; Mejalin Capsules contain calcium pantothenate and desiccated liver N. F.

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Mejalin Capsules: Bottles of 100 and 500.

The complete vitamin B complex supplement

MEAD JOHNSON & COMPANY
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in the treatment of Hypertension

Prolonged effect of mannitol hexanitrate

lowers pressure for 4 to 6 hours

New and Nonofficial Remedies: A.M.A. Council on Pharmacy and Chemistry, J. B. Lippincott, p. 243, 1953.

Marked diuretic action of theophylline

facilitates sodium excretion

Med. Times *81*:266 (Apr.) 1953.

Phenobarbital for relaxation without hypnosis

most useful for promoting daytime relaxation

J.A.M.A. *147*:1311 (Dec.) 1951.

Ascorbic acid + rutin for capillary protection

help to maintain capillary integrity

Delaware State M. J. *22*:283 (Oct.) 1950.

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BRINGS THE PRESSURE DOWN SLOWLY SAFELY

Complete Medication for the Hypertensive

Each Semhyten Capsule contains:		Phenobarbital	¼ gr. (15 mg.)
Mannitol Hexanitrate	½ gr. (30 mg.)	Rutin	10 mg.
Theophylline	1½ gr. (0.1 Gm.)	Ascorbic Acid	15 mg.

Supplied: In bottles of 100, 500 and 1000 pink-top capsules.

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Cortril tablets

brand of hydrocortisone

anti-rheumatic

anti-allergic

anti-inflammatory

indicated in:

Rheumatoid Arthritis
Osteoarthritis
Acute Rheumatic Fever
Bronchial Asthma
Allergic Dermatoses
Acute and Chronic Ocular Disorders

and other conditions responsive to adrenocortical hormone therapy, e.g., Addison's disease, intractable hay fever, drug reactions, etc.

Superior anti-rheumatic potency

In comparison with cortisone, hydrocortisone produces maximal therapeutic benefits with smaller dosage requirements, and endocrine complications are fewer and less pronounced.[1,2]

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Systemic administration of CORTRIL tablets quickly relieves active inflammatory and constitutional manifestations, often within a few hours. Crippling pain, stiffness, and swelling diminish rapidly and beneficial effects persist with continuance of therapy.

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CORTRIL tablets are a valuable adjunct in achieving enhanced function and comfort in weight-bearing joints.

When the joints involved are few in number, or when one or two joints do not respond to systemic therapy, injection of CORTRIL Acetate Aqueous Suspension directly into the joint affords remarkably effective, safe therapy.

the predominant glucocorticoid

supplied:

CORTRIL TABLETS *(hydrocortisone, free alcohol), scored, as 10 mg. tablets in bottles of 25, and 20 mg. tablets in bottles of 20.*

also available:

CORTRIL ACETATE AQUEOUS SUSPENSION
for intra-articular injection, in 5-cc. vials; 25 mg. per cc.

CORTRIL ACETATE OPHTHALMIC SUSPENSION WITH TERRAMYCIN® *5 cc., in amber bottles with sterile eye dropper; each cc. of sterile suspension provides 15 mg. hydrocortisone acetate and 5 mg.* TERRAMYCIN *hydrochloride.*

CORTRIL ACETATE OPHTHALMIC OINTMENT
in 1/8-oz. tubes in strengths of 0.5% and 2.5%.

CORTRIL ACETATE TOPICAL OINTMENT
in 1/6-oz. tubes in strengths of 1.0% and 2.5%.

Pfizer Syntex Products

references:

1. Boland, E. W.: Ann. Rheum. Dis. 12:125, 1953.
2. Boland, E. W., and Headley, N. E.: J.A.M.A. 148:981, 1952.

Pfizer PFIZER LABORATORIES *Brooklyn 6, New York*
Division, Chas. Pfizer & Co., Inc.

'TRICOLOID' brand
TRICYCLAMOL

New...

for peptic ulcer
or gastrointestinal
spasm

'TRICOLOID' brand
TRICYCLAMOL

A recently developed anticholinergic agent which has a marked effect on reducing gastrointestinal motility and spasm.

'TRICOLOID' affords relief, in most instances, within a few hours, from the gnawing pain associated with peptic ulcer.

'TRICOLOID' is recommended for the medical management of peptic ulcer and gastrointestinal spasm, as an adjunct to appropriate diet and antacids, as well as to therapy aimed at reduction of tension.

'Tricoloid' brand Tricyclamol, 50 mg. Compressed, sugar-coated

Bottles of 100

Pleasant to take

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THIS NEW REPRINT HAS THE ANSWERS TO THESE VITAL

PULMONARY FUNCTION QUESTIONS

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- What is the formula for predicting the normal MBC for both men and women.
- Is positive pressure treatment and a potent bronchodilator drug better than drugs alone?
- What are the three major mechanical factors influencing pulmonary ventilation when considering pulmonary function impairment?
- What does a marked *decrease* in oxygen uptake during step up exercise indicate?
- How can a numerical ventilation factor be derived from the timed vital capacity, the MBC and the residual percent of the total lung volume?

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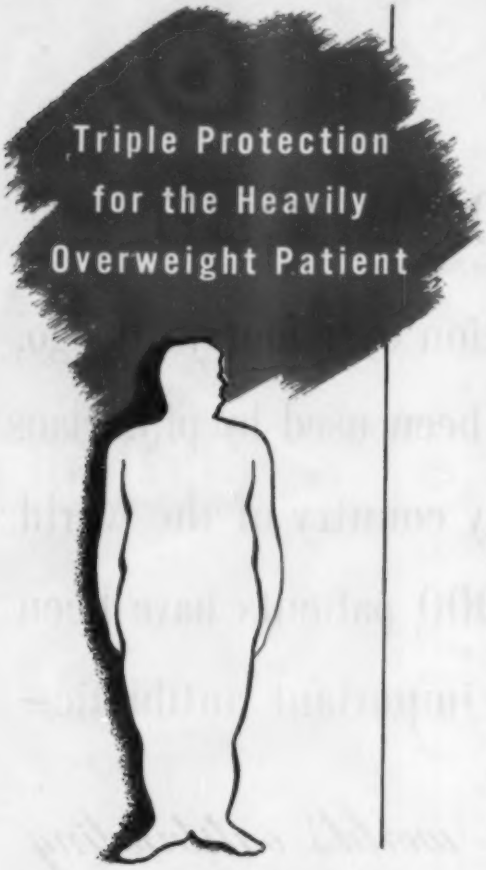

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Obocell Complex contains choline,[1] best for transporting neutral fat, and inositol, considered superior in transporting cholesterol.

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Obocell Complex supplies thiamine, riboflavin and niacinamide in amounts recommended by Zelman.[1] These vitamins are essential in intermediary carbohydrate metabolism and oxidative processes.

1. Zelman, S.: Arch. Int. Med. 90: 141, 1952.

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Each Obocell Complex capsule supplies:

d-Amphetamine Phosphate (dibasic)	5 mg.
Nicel*	100 mg.
Choline Bitartrate	200 mg.
Inositol	60 mg.
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Riboflavin	1.2 mg.
Niacinamide	8 mg.

Bottles of 50 and 500

*Irwin-Neisler's Brand of High Viscosity Methylcellulose.

Obocell Complex

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Gantricillin-300 'Roche'

...for wide-spectrum antibacterial therapy: GANTRICILLIN®-300 'Roche.' Each tablet provides 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the single, highly scluble sulfonamide.

Combined antibacterial therapy —

...with the new Gantricillin®-300 tablet 'Roche.' A convenient way of administering 300,000 units of penicillin PLUS 0.5 Gm of Gantrisin®, the single, soluble sulfonamide.

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it could be a reservoir of diarrheal infection.
Against the common diarrheas, STREPTOMAGMA brings potent antibacterial action *plus* adsorbent, demulcent and protective effects. Clinical experience with STREPTOMAGMA indicates that remission is nearly always prompt and complete.

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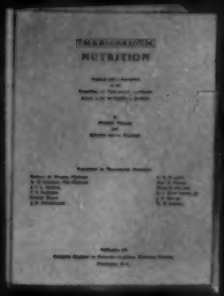
NEW NATIONAL RESEARCH COUNCIL STANDARDS*

for effective vitamin therapy



Emphasizing that regular vitamin intake is essential to productive health and that stresses such as disease and injury profoundly affect nutritional requirements, the Committee on Therapeutic Nutrition of the Food and Nutrition Board* recommends standard vitamin formulations for both maintenance and therapeutic dosage. In Panalins and Panalins-T, Mead Johnson & Company makes these authoritatively recommended formulations available to the medical profession.

Each Panalins-T Capsule supplies:

Thiamine	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Calcium pantothenate	20 mg.
Pyridoxine	2 mg.
Folic acid	1.5 mg.
Ascorbic acid	300 mg.
Vitamin B_{12}	4 mcg.

Bottles of 30 and 100.

Each Panalins capsule supplies:

Thiamine	2 mg.
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Niacinamide	20 mg.
Ascorbic acid	50 mg.
Calcium pantothenate	5 mg.
Pyridoxine	0.5 mg.
Folic acid	0.25 mg.
Vitamin B_{12}	2 mcg.
Vitamin A	5000 units
Vitamin D	400 units

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* Therapeutic Nutrition, Committee on Therapeutic Nutrition, Food and Nutrition Board, Publication 234, National Research Council.

For vitamin therapy in stress situations

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Panalins-T supplies important water-soluble vitamins in the high therapeutic potencies needed to promote optimal recovery from disease or injury. Since the body cannot store appreciable amounts of these vitamins, regular provision of generous amounts is essential.

1 or 2 Panalins-T capsules daily in:

- severe illnesses
- chronic illnesses
- injuries, including fractures
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- second or third degree burns
- previous vitamin depletion
- conditions involving a marked catabolic or anabolic response

to safeguard and maintain vitamin adequacy

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Panalins supplies protective potencies of ten vitamins needed for maintenance of the good vitamin nutrition essential to productive health.

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- patients with inadequate or irregular diets
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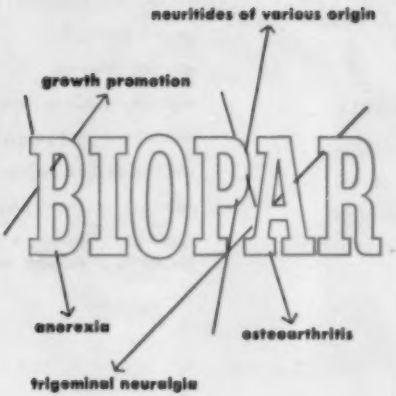
- convalescents in late stages
- patients undergoing mild physiologic and pathologic stresses

❊ *Therapeutic Nutrition, Publication No. 234, National Research Council.*

MEAD JOHNSON & COMPANY · EVANSVILLE, INDIANA, U.S.A. MEAD



with wide non-hematologic uses

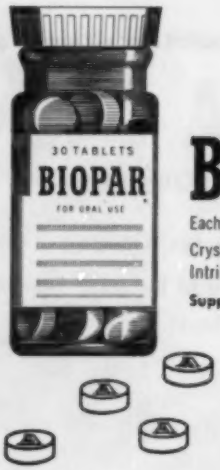
Biopar is exceedingly useful as an oral replacement for injectable vitamin B_{12} treatment, and as an adjunct to high-potency injections. A pronounced "tonic" effect is accredited to vitamin B_{12}.

BIOPAR is "intrinsically" better

A new, many times more potent Intrinsic Factor in Biopar makes possible a full therapeutic vitamin B_{12} response orally—even in the presence of partial or complete achlorhydria. The Intrinsic Factor in Biopar, many times more active than previously available intrinsic factor preparations—performs the essential functions ascribed to the classic Intrinsic Factor of Castle.

an effective oral replacement for injectable B_{12}

Oral Biopar therapy produces a full reticulocyte response and red blood cell increment in pernicious anemia, as confirmed by fourteen independent investigators (personal communications).



BIOPAR®

Each BIOPAR tablet contains:

Crystalline Vitamin B_{12} U.S.P.	6 mcg.
Intrinsic Factor	30 mg.

Supplied: Bottles of 30 tablets.

THE ARMOUR LABORATORIES

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FIRST AND ONLY

broad-spectrum antibiotic available for intramuscular use

Terramycin®

Brand of oxytetracycline

INTRAMUSCULAR

- Rapidly attained therapeutic levels
- Adequate broad-spectrum action
- For use when oral therapy is not practical or is contraindicated
- Just 100 mg. (one single-dose vial) every 8 or 12 hours is adequate for most infections in adults
- Usually well tolerated on **DEEP** intramuscular injection *(Contains procaine to minimize local tissue reaction)*
- When reconstituted, forms a *clear* solution

Supplied: In dry powder form, in single-dose, silicone-treated, "drain-clear" vials. When reconstituted by addition of 2.1 cc. of sterile aqueous diluent, each single dose (2 cc.) contains:

Crystalline Terramycin hydrochloride	100 mg.
Magnesium chloride	100 mg.
Procaine hydrochloride	2% w/v

Pfizer

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Upjohn

one dose
lasts
2 to 4 weeks

Depo-Testosterone
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CYCLOPENTYLPROPIONATE

Each cc. contains:
Testosterone Cyclopentylpropionate .....50 mg. or 100 mg.
Chlorobutanol.....5 mg.
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50 mg. per cc. available in 10 cc. vials
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The Upjohn Company, Kalamazoo, Michigan

SOLUBILITY is a measure of SUITABILITY

Of the four leading sulfonamides prescribed in infections of the urinary tract, "Thiosulfil" has been demonstrated to be the most soluble. It is this greater solubility plus high bacteriostatic activity and low acetylation rate which make

"THIOSULFIL"®

the safest and most effective sulfonamide yet presented for

urinary tract infections

- Rapid transport to site of infection for early and effect[illegible]rinary concentration
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"THIOSULFIL"®
brand of sulfamethylthiodiazole

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No. 914 —
0.25 Gm. per 5 cc.
Bottles of 4 and 16 fluidounces

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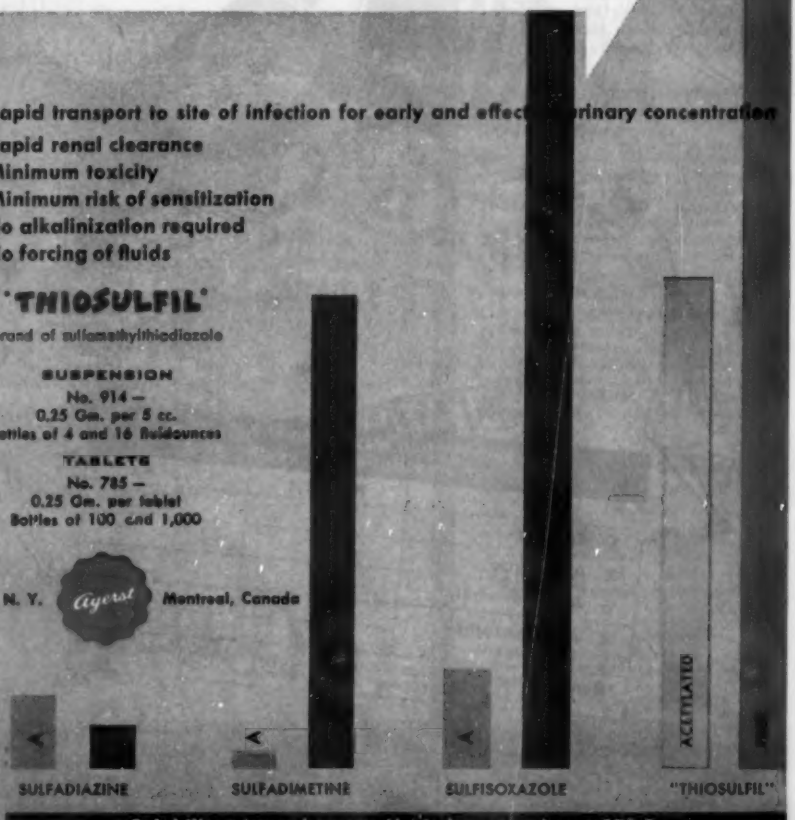
0.25 Gm. per tablet
Bottles of 100 and 1,000

New York, N. Y. Ayerst Montreal, Canada



Solubility comparison at pH 6 in human urine at 37° C.

AD12

only Kolantyl gives him this four way

Compare the four way action of Kolantyl with your prescription for peptic ulcer.

	Kolantyl	Your Rx
1 Antacid	✓	
2 Antipeptic	✓	
3 Antispasmodic*	✓	
4 Antilysozyme-Demulcent	✓	

*Bentyl — Merrell's distinctive antispasmodic that is more effective than atropine — free from "belladonna backfire".

The Wm. S. Merrell Company... *Pioneer in Medicine*

relief of peptic ulcer

controls *four* important etiologic factors

Every ulcer patient you see wants RELIEF—*prompt relief.* Only Kolantyl® provides these four therapeutic approaches to peptic ulcer: antacid, antipeptic, antispasmodic and antilysozyme-demulcent.

Your Kolantyl prescription represents one of the most complete peptic ulcer preparations available today. Give your next ulcer patient economical four way relief... prescribe good-tasting *Kolantyl.*

Kolantyl

Appearance of active duodenal ulcer after 12 weeks ambulatory treatment with diet and Kolantyl, marked clinical improvement.[1]

Prescribe Kolantyl for Prompt Relief of peptic ulcer, gastritis, hyperacidity.

action:

Antacid (magnesium oxide, aluminum hydroxide) for almost immediate, prolonged neutralization of acid without rebound.

Antipeptic (sodium lauryl sulfate) inhibits necrotic action of pepsin and lysozyme.

Antispasmodic (Bentyl) relieves painful spasm comfortably; superior to atropine.[2]

Demulcent (methylcellulose) provides a protective coating of the ulcerated area.

composition:

Each tablet or 10 cc. Kolantyl Gel contains:

Bentyl Hydrochloride	5 mg.
Aluminum Hydroxide Gel	400 mg.
Magnesium Oxide	200 mg.
Sodium Lauryl Sulfate	25 mg.
Methylcellulose	100 mg.

dosage:

Prescribe two to four teaspoonfuls Kolantyl Gel or two tablets (chewed for more rapid action) every 3 hours, or as needed for relief.

Gel supplied in 12 oz. bottles — Tablets in bottles of 100 and 1000.

1. HUFFORD, A. R.: MICH. STATE MED. SOC. 49:1208, 1950.

2. MCHARDY, G. AND BROWNE, D.: BRIT. MED. J. 45:1139, 1952.

KOLANTYL® "BENTYL" T. M.

for 125 Years

New York
CINCINNATI
St. Thomas, Ontario

Merrell
Since 1828

3 steps to better diagnosis

in Vascular Disturbances

#1 The Newest Development in Sphygmomanometers

THE MANUELL ANEROID combines a sturdy aneroid manometer with a new and long needed, practical design feature. The manometer is attached directly to the bulb held in the hand of the physician—where it belongs. Hooking or hanging the dial from the cuff on the patient's arm is no longer necessary. Minimum of patient anxiety and apprehension since only the physician can see the dial.

Light weight—compact—packs and carries easily in a soft leather case—suitable for office use and unexcelled for outside calls—available from your dealer

List Price—with wrap-around cuff **$40.00**

Other Propper Sphygmomanometers include wall and desk model mercurials and regular aneroids of high quality at economy prices.

All models available with wrap-around or hook-on cuff.

#2 Propper Oscillometer (Pachon)

Goes beyond blood pressure—provides the physician with further diagnostic and clinical information on peripheral vascular diseases—reveals impaired arterial circulation by completely objective, numerical *measurement* of vascular volume which can be compared with recognized and published norms for all parts of upper and lower extremities. Quickly verifies clinical picture indicative of certain diseases and provides a progressive record of the effect of the treatment. This, in addition to routine diastolic, systolic and mean blood pressures which can be obtained from the same instrument *without the use of a stethoscope.*

List Price **$87.50**

#3 Propper Oscillograph

For the physician who desires the ultimate in vascular diagnosis and case history. The Propper oscillograph gives *simultaneous* pulse readings of two extremities—and provides a permanent, written record of the test. For comparative studies and complete case histories the oscillograph is as important as the EKG. The most complete equipment—in one handy case—available only from Propper. For full information, write to:

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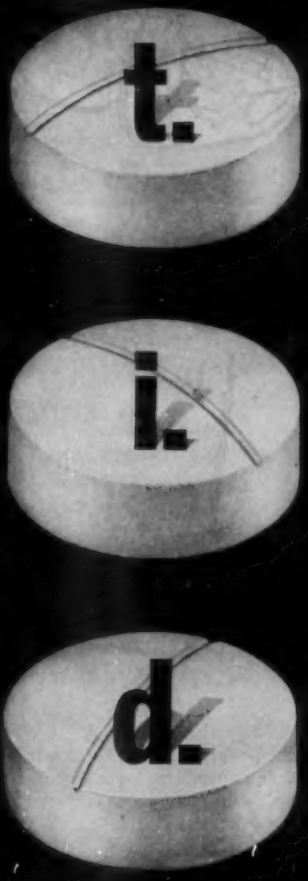
All Propper Specialized Instruments Are Unconditionally Guaranteed! Certificates of Warranty supplied with all instruments.

1st choice for oral penicillin therapy

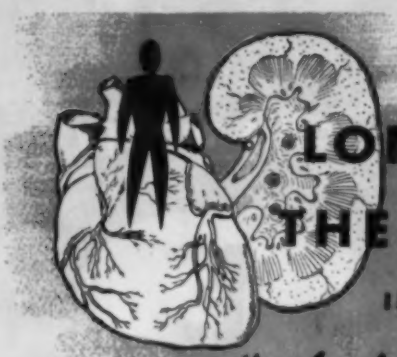
just 1 or 2 tablets



Pentids

Squibb 200,000 Unit Penicillin G Potassium Tablets

SQUIBB



LONALAC MAKES THE DIFFERENCE

IN LOW SODIUM DIETS

—with Lonalac...

adequate protein

Rx

200 mg. sodium diet
Meat, 1 serving
Egg, 1
Low sodium bread
Cereal
Vegetables
Fruits

Lonalac — 1 quart liquefied — to be used like milk

Average protein — 80 Gm.
Average sodium — 200 mg.

Rx

200 mg. sodium diet
Meat, 1 serving
Egg, 1
Low sodium bread
Cereal
Vegetables
Fruits

Average protein — 50 Gm.
Average sodium — 180 mg.

—without Lonalac...

inadequate protein

Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened . . . since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

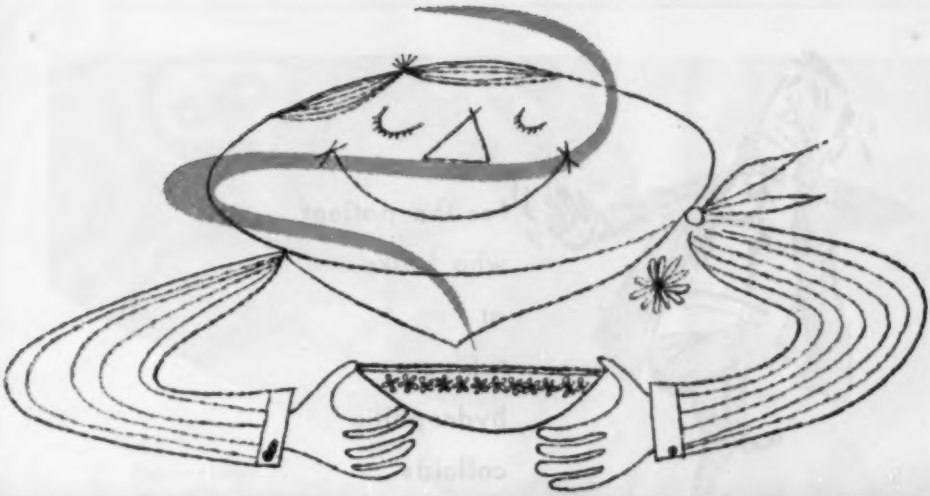
Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

The low sodium, high protein food

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A. MEAD



salt-free needn't mean flavor-free

DIASAL is enthusiastically endorsed by low-salt dieters for the zest and flavor it gives to pallid, sodium-restricted meals. So closely does it match the appearance, texture and taste of table salt that patient adherence to your diet instructions is virtually assured.

DIASAL contains only potassium chloride, glutamic acid and inert ingredients ... no sodium, lithium, or ammonium. It may be used safely for extended periods, both at the table and in cooking. Because of its potassium, DIASAL may be a valuable prophylactic against potassium depletion.

DIASAL®

packaging: available in 2-ounce shakers and 8-ounce bottles. Send for liberal supplies of tasting samples and low sodium diet sheets for your patients.

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for the patient
who balks
at
taking
hydrophilic
colloids

. . . prescribe

L.A. FORMULA

in milk or
orange juice

L.A. FORMULA

a bulk producer
unsurpassed
for
patient acceptance

L. A. FORMULA — *50% Plantago ovata concentrate dispersed in lactose and dextrose and refined to a unique particle size.*

Available—7 and 14 oz. containers. Samples on request.

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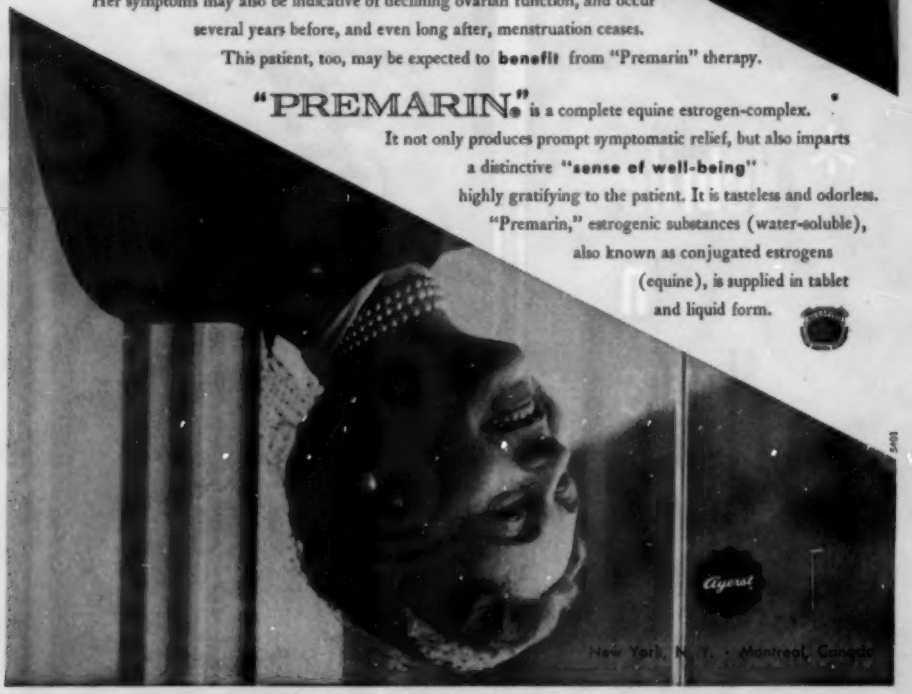
For every patient
with clearcut menopausal
symptoms such as **hot flushes,**
there's another patient with symptoms less clearly defined
yet just as distressing . . . headaches,
insomnia, mental and physical fatigue.
Her symptoms may also be indicative of declining ovarian function, and occur
several years before, and even long after, menstruation ceases.
This patient, too, may be expected to **benefit** from "Premarin" therapy.

"PREMARIN" is a complete equine estrogen-complex.
It not only produces prompt symptomatic relief, but also imparts
a distinctive "**sense of well-being**"
highly gratifying to the patient. It is tasteless and odorless.
"Premarin," estrogenic substances (water-soluble),
also known as conjugated estrogens
(equine), is supplied in tablet
and liquid form.



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BASIC chemically

The structure of this ***newest*** antibiotic represents a nucleus of modern broad-spectrum antibiotic activity

BASIC clinically

This ***newest*** broad-spectrum antibiotic has a wide range of action against respiratory, gastrointestinal, soft-tissue, urinary and mixed bacterial infections due to pneumococci, streptococci, staphylococci and other gram-positive and gram-negative organisms.

"Data thus far available would indicate that the use of tetracycline is accompanied by a significantly lower incidence of gastrointestinal symptoms . . ."

This ***newest*** broad-spectrum antibiotic may often be used with good success in patients in whom resistance or sensitivity to other forms of antibiotic therapy has developed.

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brand of TETRACYCLINE

BASIC among broad-spectrum antibiotics

supplied: TETRACYN HYDROCHLORIDE TABLETS *(sugar coated)*
250 mg., 100 mg., 50 mg.

TETRACYN HYDROCHLORIDE INTRAVENOUS
Vials of 250 mg. and 500 mg.

TETRACYN ORAL SUSPENSION *(amphoteric)*
(chocolate flavored)
Bottles of 1.5 Gm.; provides 250 mg.
per 5 cc. teaspoonful.

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J. B. ROERIG AND COMPANY, Chicago 11, Illinois

What's so *different* about the Viso-Cardiette?

THESE ARE THE COMPANY POLICIES

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SANBORN SPECIALIZES. Sanborn's *primary* and *major* interest in the medical field for the past 35 years has been the design, manufacture, and servicing of electrocardiographs. Sanborn men can therefore *concentrate* on your interest in this type of equipment.

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ECG DESIGN KNOWLEDGE. Sanborn's 30 years of specialization and intimate contact with the profession's heart testing needs results in a *complete* and *concentrated knowledge* of electrocardiograph manufacture.

EXTRA BENEFITS. These stem from the Sanborn "direct-to-you" policy, and include: the bi-monthly "Technical Bulletin", which is sent free of charge to every owner; the 15-day, no-obligation, try-before-you-buy plan; and the opportunity to deal *directly* with the maker of your electrocardiograph.

EXTENSIVE COVERAGE. The need to keep a *close contact* with Sanborn owners, and those about to be, requires a *wide* network of offices. Sanborn has thirty, one of them near you!

Because Sanborn DEPENDS on your satisfaction, YOU can depend on Sanborn people and Sanborn products. Descriptive literature which tells more about the Viso-Cardiette and the 15-day trial plan is available on request.

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195 Massachusetts Avenue, Cambridge 39, Massachusetts

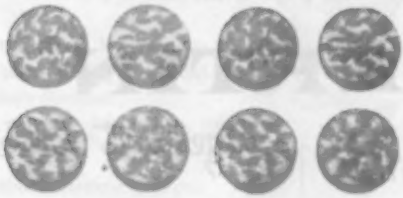
WHICH WOULD *YOUR* PATIENTS PREFER?

16 **ONE-HALF GRAM** ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS

or only **8**

AMCHLOR

ONE GRAM ENTERIC-COATED
AMMONIUM CHLORIDE TABLETS *(Brewer)*



"Easy-to-swallow" **AMCHLOR** is processed in such a manner that each enteric-coated tablet contains 1 Gram of ammonium chloride and yet is not much larger than the 7½ gr. enteric-coated tablet. Thus the same dose can be given with only one-half the number of tablets.

FROM COAST TO COAST both physicians and patients are showing a decided preference for **AMCHLOR.**

SUPPLIED *bottles of* 100, 500 and 1000

The next time you prescribe ammonium chloride specify—

AMCHLOR – Brewer

THE ONE GRAM enteric-coated tablet of ammonium chloride for your patients' convenience!

For samples just send your Rx blank marked — 7AM

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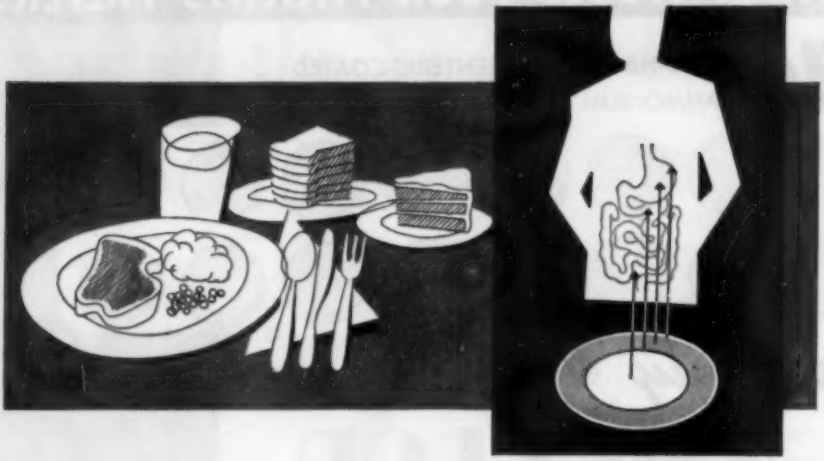


effective aid to digestion
and assimilation of foods

CONVERTIN®

digestant tablets

Special layered construction ensures separately timed action of essential digestants for maximum therapeutic effect

Each CONVERTIN tablet provides:
a sugar-coated outer layer containing
Betaine Hydrochloride . 130.0 mg.
(Equiv. 5 minims Diluted Hydrochloric Acid U.S.P.)
Oleoresin Ginger . . . . . 1/600 gr.
surrounding an enteric-coated core of
Pancreatin . . . . . 62.5 mg.
(Equiv. 250 mg. U.S.P.)
Desoxycholic Acid . . . . 50.0 mg.
Chlorophyllin . . . . . 10.0 mg.

DOSAGE: 2 tablets with or just after meals; clinical experience has shown that dose may be reduced, usually after first week, at physician's discretion.

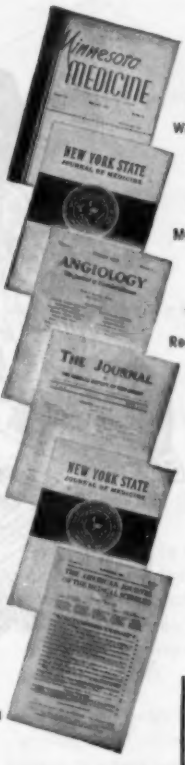
Convertin aids protein digestion through the release of HCl from betaine hydrochloride and through the subsequent action of the pancreatic enzyme, trypsin.

Convertin aids carbohydrate digestion through the action of the pancreatic enzyme, amylopsin.

Convertin aids fat digestion through the action of desoxycholic acid (a pure bile acid) and the pancreatic enzyme, steapsin. And for patient-comfort . . . CONVERTIN contains the carminative, oleoresin ginger.

B. F. ASCHER & COMPANY, INC.
Ethical Medicinals
KANSAS CITY, MO.

Available on prescription at leading pharmacies in bottles of 24 and 500 tablets.



"A powerful vasodilator effect."
White, S. M.: 33:133, 1950

"Toxic effects . . . minimal."
Murphy, J. R.: 51:2407, 1951

"Safely given over prolonged periods."
Redisch, W., and Brandman, O.: 1:312, 1950

"Remarkable results in vasospastic disorders . . . Buerger's disease . . . chronic trench foot."
Redisch, W.: 46:368, 1949

"More effective . . . in arteriosclerosis obliterans. Angina of effort markedly diminished."
Richter, I. H.; Fogel, M.; and Fabricant, H.: 51:1303, 1951

"No effect upon systemic blood pressure or cardiac rate."
Crosby, R. M. N.: 225:61, 1953

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'Roche'

RONIACOL ELIXIR
50 mg per teaspoon (4 cc)
Bottles of 16 fl oz, 1 gal

RONIACOL TARTRATE TABLETS
50 mg per scored tablet
Bottles of 100, 500, 1000

Roniacol® — brand of beta-pyridyl carbinol

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Heard at the staff meeting . . .

increases the usefulness of oral aminophylline

send for detailed literature and sample

THE S. E. MASSENGILL CO.

BRISTOL, TENNESSEE

In the form of AMINODROX, three out of four patients can be given therapeutically effective *oral* doses of aminophylline.

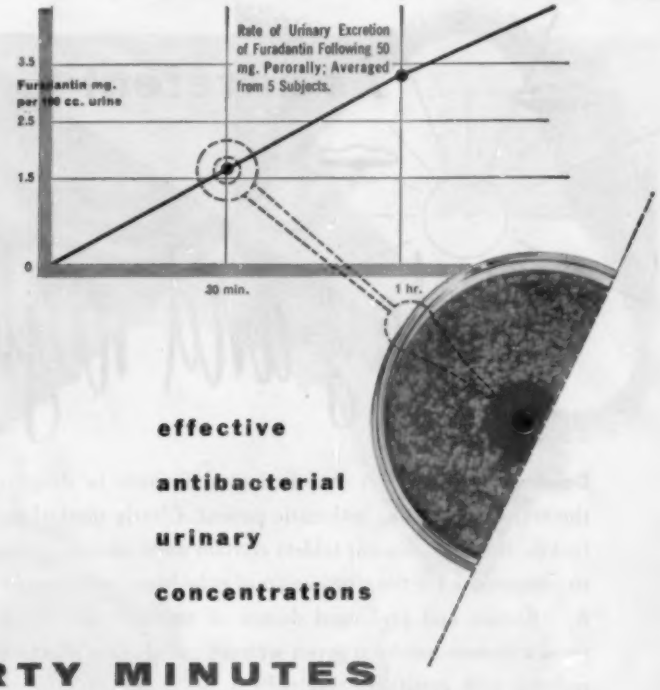
This is possible with AMINODROX because gastric disturbance is avoided.

How congestive heart failure, bronchial and cardiac asthma, status asthmaticus and paroxysmal dyspnea can be treated successfully with *oral* aminophylline in the form of AMINODROX.

Aminodrox Tablets contain 1 1/2 gr. aminophylline with 2 gr. activated aluminum hydroxide.

Aminodrox-Forte Tablets contain 3 gr. aminophylline with 4 gr. activated aluminum hydroxide.

Also available with 1/4 gr. phenobarbital.



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IN THIRTY MINUTES

So remarkable is the affinity of Furadantin for the urinary tract that the urine becomes actively antibacterial within 30 minutes after ingestion, as shown by urinary concentrations and agar plate tests.

Furadantin exhibits an extensive range of antibacterial activity against both gram-positive and gram-negative urinary tract invaders.

Scored tablets of 50 & 100 mg.

IN ACUTE AND CHRONIC URINARY INFECTIONS

FURADANTIN®

BRAND OF NITROFURANTOIN, EATON

ACCEPTED COUNCIL ON PHARMACY AND CHEMISTRY AMERICAN MEDICAL ASSOCIATION

EATON LABORATORIES Inc.

NORWICH, NEW YORK

THE NITROFURANS—A UNIQUE CLASS OF ANTIMICROBIALS O_2N R PRODUCTS OF EATON RESEARCH

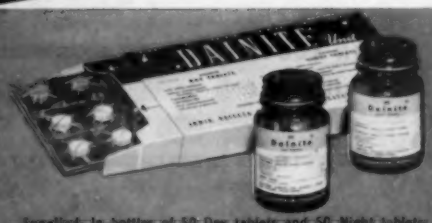
Dainite tablets meet the distinct difference in drug requirement of the active and resting asthmatic patient. Clearly marked to preclude confusion, the Dainite *night* tablets contain more aminophylline and sedative to compensate for the elimination of ephedrine, and assure a restful night. An effective and prolonged dosage of aminophylline protected by anti-nausea factors has been given without gastric side effects to hundreds of patients with gratifying results.[1-5]

References: (1) Segal, M. S., et al.: Quart. Rev. Allergy & Applied Immunol. 6: 399-415, 1952; (2) Barach, A. L.: Med. Rec. & Ann. 46: 323-331, 1952; (3) Segal, M. S., et al.: Trans. Nat. Tbc. Assn., 48th Ann. Meet., 1952, pp. 374, 385; (4) Segal, M. S., and Dulfano, M. J.: GP 7: 58, 1953; (5) Segal, M. S., and Dulfano, J. M.: Modern Med. Monographs, New York, Grune & Stratton, 1953, No. 8, pp. 79-80.

In bronchial asthma

Dainite tablets

Each DAY Tablet contains:		Each NIGHT Tablet contains:
....	Phenobarbital	⅜ gr.
¼ gr.	Sodium Pentobarbital	½ gr.
3 gr.	Aminophylline	4 gr.
¼ gr.	Ephedrine HCl	
¼ gr.	Ethyl Aminobenzoate	¼ gr.
2½ gr.	Aluminum Hydroxide	2½ gr.
Give t.i.d. a.c.		Give at 10 P.M.



Supplied: In bottles of 50 Day tablets and 50 Night tablets; also supplied as the Dainite Unit containing 48 Day tablets and 14 Night tablets in a unique dispensing package.

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

PHOTOGRAPH BY VICTOR KEPPLER

Penicillin—in her favorite beverage

PENALEV®

SOLUBLE TABLETS POTASSIUM PENICILLIN G

Readily soluble in milk, fruit juice, infant formulas, PENALEV is a highly agreeable way to give penicillin to your young patients. "The rheumatic child who should receive routine year-round penicillin prophylaxis,"[1] won't object to penicillin when she can drink it.

PENALEV is effective in all infections where oral penicillin is indicated. Its solubility makes it a useful form for regulation of dosage. Convenient for prescription compounding, too.

Quick Information: PENALEV is supplied in soluble tablets of 50,000, 100,000, 200,000, 250,000, 500,000, 1,000,000 units of potassium penicillin G each. Dosage depends on type and severity of the infection.

Reference: 1. J.A.M.A. 151:347, 1953.

Gitaligin®

AMORPHOUS GITALIN

Further Evidence of Its Wide Margin of Safety

"The clinical application of the wide difference between toxic and therapeutic dose in gitalin is an important advance in the pharmacology of cardiac glycosides."

Dimitroff, S.P.; Griffith, G.C.; Thorner, M.C., and Walker, J.: Clinical Evaluation of Gitalin in the Treatment of Congestive Heart Failure, Annals of Int. Med. **39**:1189 (Dec.) 1953.

"...our observations indicate that the average digitalizing and maintenance doses of gitalin are approximately one-third of the respective toxic doses."

Weiss, A., and Steigmann, F.: Gitalin in the Treatment of Congestive Heart Failure: A Clinical Study, Amer. J. Med. Sc. (Feb.) 1954.

This wide margin of safety reported by the above investigators, and based on their carefully evaluated clinical studies, helps confirm previous findings:

Batterman, R.C., et al.: Studies with Gitalin (amorphous) for the Treatment of Patients with Congestive Heart Failure, Am. Heart J. **42**:292 (Aug.) 1951.

Batterman, R.C., et al.: The Therapeutic Range of Gitalin (amorphous) Compared with Other Digitalis Preparations, Circulation **5**:201 (Feb.) 1952.

Because of its short latent period, Gitaligin acts more rapidly than digitalis leaf or digitoxin, and because of its moderate rate of dissipation it is also excreted more rapidly. It thus provides maximum ease and safety of maintenance.

Gitaligin is accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

Simple dosage equivalent: Use 0.5 mg. (1 tablet) Gitaligin for each 0.1 Gm. (1½ gr.) digitalis leaf. Gitaligin is supplied in 0.5 mg. tablets, scored—bottles of 30 and 100.

White Laboratories, Inc., Kenilworth, N.J.

EVENTUALLY, you may be riding herd on his irregular eating habits and probably, prescribing a potent, B complex supplement like SUR-BEX or SUR-BEX WITH VITAMIN C.

Compressed, easy to swallow, each SUR-BEX tablet provides six important B vitamins, plus liver fraction and brewer's yeast. SUR-BEX WITH C adds five times the minimum daily requirement of ascorbic acid.

No trace of liver odor in these triple-coated, vanilla-flavored tablets. Daily prophylactic dose is one tablet. Two or more for severe deficiencies. In bottles of 100, 500 and 1000. Abbott

Each SUR-BEX Tablet contains:

Thiamine Mononitrate	5 mg.
Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	2 mcg.
Pantothenic Acid (as calcium pantothenate)	10 mg.
Liver Fraction 2, N.F.	0.3 Gm. (5 grs.)
Brewer's Yeast, Dried	0.15 Gm. (2½ grs.)

Sur-bex with Vitamin C contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors above.

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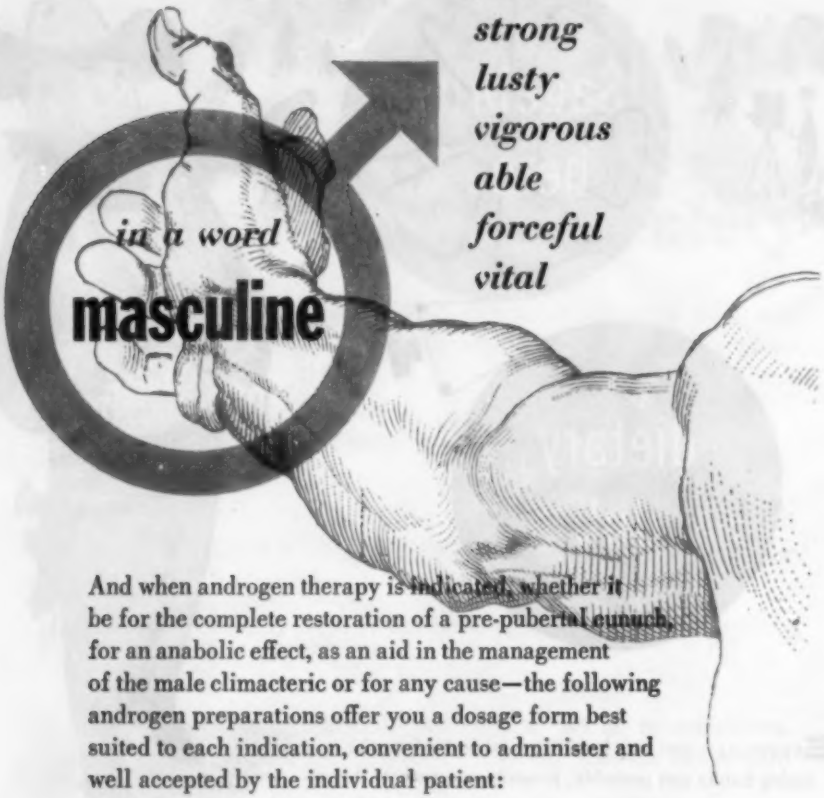
SUR-BEX

(Abbott's Vitamin B Complex Tablets)

or **SUR-BEX with C**

5-139



virile
strong
lusty
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And when androgen therapy is indicated, whether it be for the complete restoration of a pre-pubertal eunuch, for an anabolic effect, as an aid in the management of the male climacteric or for any cause—the following androgen preparations offer you a dosage form best suited to each indication, convenient to administer and well accepted by the individual patient:

SYNANDROL* brand of testosterone propionate in sesame oil: 25 mg., 50 mg. and 100 mg./cc. in 10 cc. multiple-dose vials and in single-dose Steraject® disposable cartridges.

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SYNANDROTABS* brand of methyltestosterone tablets, for oral use: 10 mg. and 25 mg., bottles of 25 and 100.

SYNANDRETS* brand of testosterone transmucosal tablets, for absorption by the transmucosal route: 10 mg., bottles of 25 and 100; 25 mg., bottles of 25.

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This rheumatic patient is safer on

Armyl

because Armyl supplies vitamin C in higher potency

In Armyl, vitamin C potencies are higher to prevent salicylate-induced ascorbic acid deficiency. Thus, Armyl offers definite antihemorrhagic protection. Furthermore, the high vitamin C content of Armyl helps to raise therapeutic salicylate blood levels.

Armyl

Armyl . . . Armyl with ⅛ gr. Phenobarbital . . . Armyl Sodium-Free . . . Armyl Sodium-Free with ⅛ gr. Phenobarbital

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modern criteria of good digitalis therapy

1. pure active principle
2. complete absorption
3. rapid onset of action
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digitaline nativelle®

conforms to the rigid criteria of a modern cardiotonic and provides oral, I.M., and I.V. forms for flexibility of dosage

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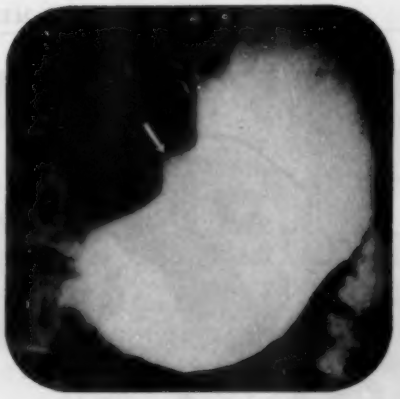

Fig. 3, Case 103 before therapy.

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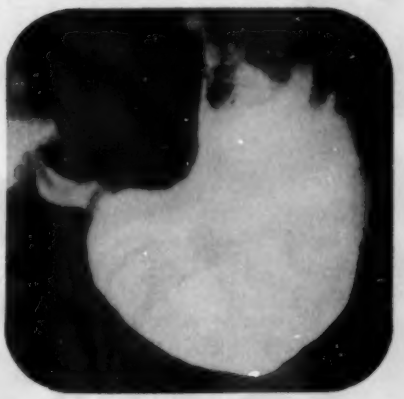

Fig. 6, Case 103 after 4 months PRANTAL therapy.
* Heineken, T. S.: Rev. Gastroenterol. 20:829, 1953.

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ANNALS OF
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GAUCHER'S DISEASE IN 29 CASES: HEMATOLOGIC COMPLICATIONS AND EFFECT OF SPLENECTOMY *

By ALAN S. MEDOFF, M.D., and EDWIN D. BAYRD, M.D.,
Rochester, Minnesota

GAUCHER'S disease is a rare, heredofamilial disorder of cerebroside metabolism characterized clinically in the adult by an insidious onset, splenomegaly, pigmentation, pingueculae, a protracted course, and usually some hematologic abnormality. In an effort to determine the incidence and nature of these hematologic variations and, in addition, to study the effects of splenectomy on patients having this disease, we have reviewed all proved cases of Gaucher's disease seen at the Mayo Clinic through the year 1950. Twenty-nine such cases were found (tables 1 and 2). Since the majority of clinical reports dealing with this disease contain only small numbers of cases, it also was thought that the experience with a larger group should be made available. In all cases the diagnosis was established by aspiration of sternal marrow, splenic puncture, examination of splenic tissue after splenectomy, or by necropsy.

CLINICAL FEATURES

In the early part of the twentieth century the general opinion was that more females than males had Gaucher's disease, but later studies suggested that the distribution between sexes is equal.[1, 2] In 15 of the 29 cases reported herein the patients were female and in 14 they were male. The youngest was two and one-half years of age and the oldest 56 years at the time of their first visit to the clinic. It is of interest to note that nine patients were 40 years of age or older. The number of patients with Gaucher's disease in the fourth, fifth and sixth decades of life has not been

* Received for publication August 10, 1953.
From the Division of Medicine of the Mayo Clinic, Rochester, Minnesota.

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TABLE I
Essential Data in 29 Cases of Gaucher's Disease

Case	Race and Sex	First Visit to Clinic		Age at Onset	Initial Manifestations	Family History	Diagnosis		Physical Findings
		Age, yr.	Date				Age of Patient, yr.	Year	
1	Jewish M	15	1940	18 mo.	Splenomegaly, anemia, easily bruised	Negative	4	1929	Splenomegaly, hepatomegaly, hyperopia
2	Jewish M	42	1944	32 yr.	Splenomegaly (asymptomatic)	Negative	42	1944	Splenomegaly, hepatomegaly, pretibial edema
3	Jewish F	41	1943	12–14 yr.	Splenomegaly (asymptomatic), easily bruised	Negative	41	1943	Splenomegaly, hepatomegaly, pingueculae, pigmentation of skin
4	Jewish F	42	1941	28 yr.	Pain left hip	One brother died in infancy	42	1941	Splenomegaly, pingueculae, hepatomegaly, pigmentation of skin
5	Jewish M	20	1940	7 yr.	Gastrointestinal upsets	Negative	20	1940	Splenomegaly, hepatomegaly
6	American F	43	1950	36 yr.	Fatigue, anemia, easily bruised	Negative	43	1950	Splenomegaly, hepatomegaly, ecchymoses
7	Jewish M	37	1945	Birth	Splenomegaly	Negative	37	1945	Splenomegaly, hepatomegaly, pigmentation of skin, enlarged heart
8	Italian F	15	1948	5 yr.	Splenomegaly, pulmonary tuberculosis, easily bruised	Relative of mother showed splenomegaly at necropsy in 1923	15	1948	Splenomegaly, hepatomegaly, pingueculae
9	Jewish M	14	1947	12 yr.	Pain left knee	Negative	12	1945	Splenomegaly, hepatomegaly, pigmentation of skin
10	Jewish M	50	1925	35 yr.	Painless mass left upper quadrant, easily bruised	Sister with splenomegaly	Made prior to 1925		Splenomegaly, hepatomegaly, pingueculae, pigmentation of skin, ecchymoses

TABLE I—*Continued*

Case	Race and Sex	First Visit to Clinic		Age at Onset	Initial Manifestations	Family History	Diagnosis		Physical Findings
		Age, yr.	Date				Age of Patient, yr.	Year	
11	Polish M	14	1938	9 yr.	Attacks of icterus lasting 2 to 3 days, easily bruised	Negative	14	1938	Splenomegaly, hepatomegaly, pingueculae, pigmentation of skin
12	American M	49	1938	29 yr.	Easily bruised, fatigue	Negative	49	1938	Splenomegaly, hepatomegaly, pigmentation of skin, icterus, ecchymoses
13	Unknown M	4	1938	4 yr.	Upper respiratory infection	Negative	4	1938	Splenomegaly, hepatomegaly, adenopathy, general maculopapular skin rash
14	Unknown F	4	1947	2 yr.	Recurrent and persistent epistaxis	Negative	3	1946	Splenomegaly, hepatomegaly, pigmentation of skin around neck
15	Peruvian M	12	1941	7 yr.	Splenomegaly and vague abdominal pains	Negative	12	1941	Splenomegaly, hepatomegaly
16	Jewish F	10	1926	Unknown	Unknown. In 1926 complained of bone lesions	Negative	3	1919	Hepatomegaly (spleen out)
17	Jewish F	26	1927	7 yr.	Splenomegaly, anemia, fatigue, easily bruised	Some relatives may have had Gaucher's disease	26	1927	Splenomegaly, hepatomegaly, pingueculae, pigmentation of skin
18	Jewish F	33	1928	Unknown	Unknown. Came to clinic for nasal boils	Negative	33	1928	Splenomegaly, pingueculae
19	Jewish M	31	1931	27 yr.	Pain left upper quadrant. Splenomegaly discovered on roentgenogram of stomach	Negative	32	1932	Splenomegaly, hepatomegaly

TABLE I—*Continued*

Case	Race and Sex	First Visit to Clinic		Age at Onset	Initial Manifestations	Family History	Diagnosis		Physical Findings
		Age, yr.	Date				Age of Patient, yr.	Year	
20	Jewish F	39	1933	30 yr.	Splenomegaly (asymptomatic), easily bruised	Brother had splenomegaly	39	1933	Splenomegaly, hepatomegaly
21	Jewish F	30	1932	27 yr.	Fatigue, anorexia	Negative	30	1932	Splenomegaly, hepatomegaly, purpura
22	Jewish F	56	1950	31 yr.	Splenomegaly, anemia, easily bruised	Negative	48	1942	Splenomegaly, ecchymoses
23	Greek M	10	1947	9 yr.	Splenomegaly, upper respiratory infection, easily bruised	Paternal grandfather and cousin had large abdomens	10	1947	Splenomegaly, hepatomegaly
24	German F	2½	1948	15 mo.	Weakness, strabismus, retarded development	Younger brother has Gaucher's disease	2½	1948	Splenomegaly, hepatomegaly
25	Jewish F	19	1950	Childhood	Anemia, fatigue	Negative	14	1945	No splenomegaly (spleen removed elsewhere)
26	Unknown F	20	1949	3 yr.	Enlarged abdomen, easily bruised	Negative	3	1932	Splenomegaly, pinguecculae, pigmentation of skin, pallor
27	American M	40	1935	32 yr.	Splenomegaly, exhaustion, fatigue	Negative	40	1935	Splenomegaly, pallor, hypertension, ecchymoses
28	American M	52	1922	42 yr.	Splenomegaly, weakness	Negative	53	1923	Splenomegaly, pigmentation of skin
29	American F	36	1923	In infancy 2 yr.	Hepatomegaly	Negative	36	1923	Splenomegaly, hepatomegaly

TABLE II

Peripheral Blood Findings and Results of Roentgenologic Examinations for 14 Patients Not Splenectomized

Case	Hemoglobin, gm.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Platelets, thousands per cu. mm.	Reticulocytes, per cent	BSP Test, Grade	Serum Bilirubin	Roentgenologic Examinations
1	9.6	4.71	5.9					Erlenmeyer flask deformities, both femora
2	11.9	3.83	4.6	43	2.8	0	0.9(I)*	Cystoid defects both femora typical of Gaucher's disease
3	8.5–10.5	3.19–4.70	1.5–5.5	57–64	2.7–4.3	0	0.5(I)	Distal expansion and rarefaction of femora
4	11.9	4.52	7.8			1	3.5(I)	Erlenmeyer flask deformities both femora. Thinning of cortex of distal portions of humeri, tibiae and fibulae
5	13.1	5.00	6.2			0	1.1(I)	No evidence of changes in the femora and tibiae
6	10.3	3.7	5.2	60	6.1	0	1.2(I)	Changes typical of Gaucher's disease in femora and humeri
7	12.5	4.09	2.2	28 53		1	1.2(D)† 1.2(I)	Erlenmeyer flask deformities femora
8	8.0	2.87	3.4	42				None reported
9	11.6	4.4	7.5	124				Changes typical of Gaucher's disease in both femora
10	54%‡	3.26	7.0	136		"Normal"	"Normal"	None reported
11	8.7	4.49	4.7			0	1.2(I)	Widening of distal femora and thinning of cortex
12	12.1	3.25	3.1	64				No evidence of changes in the femora
13	11.4	4.75	5.0					Slight osteoporosis—femora
14	10.2			73–92				No evidence of change

* Indirect.
† Direct.
‡ Dare.

generally appreciated. In this group of 29 patients, three were in the sixth decade of life, six in the fifth, six in the fourth, three in the third, eight in the second, and only three in the first at the time of their first visit to the clinic. None of the patients proved to have so-called acute infantile Gaucher's disease.

Sixteen patients were of Jewish extraction; five stated their nationality as "American," and one each was of Polish, German, Peruvian, Greek and Italian origin. In three cases no statement had been made regarding the patient's racial background. It seems likely from other data at our disposal that on more careful questioning a greater number of patients would have been noted to be of Jewish ancestry.

In only one case was a positive family history of Gaucher's disease elicited. Six patients, however, mentioned that some member of their

family had splenomegaly of unknown origin. The number of cases in which it was due to Gaucher's disease is conjectural.

In every instance the onset of the disease was gradual. Vague feelings of weakness, fatigue, exhaustion and tiredness over long periods preceded, and later accompanied, the more definite signs of splenomegaly, hepatomegaly and changes in the skin. Easy bruising and epistaxis were presenting complaints in 12 cases. The commonest complaints, however, were those referable to a gradually enlarging spleen. Generally speaking, splenomegaly did not cause much discomfort in the early stages of the disease, and most patients were only aware of a painless mass in the left upper quadrant of the abdomen. In the later stages, the spleen usually became so large that distress from it was noted by every patient. Pain over a region of osseous involvement was reported by two patients whose roentgenograms exhibited evidence of changes typical of Gaucher's disease, but not by all of those so afflicted.

Splenomegaly, present in all of the cases studied, varied from a palpable splenic tip to a huge spleen that occupied almost all of the abdomen. Splenomegaly is ordinarily considered to be a constant finding in Gaucher's disease, but in at least one case in the literature its presence was notably absent.[3] Hepatomegaly is a less constant occurrence. It was noted in 23 of our 29 cases (79 per cent). Even in the presence of a palpable and enlarged liver, results of the bromsulfalein liver function test were normal, an observation also noted by Gordon.[4] The values for indirect reacting serum bilirubin tended to be slightly higher than normal but were not greatly elevated at any time. Direct reacting bilirubin was noted in only one instance. Pigmentation of the skin was present in 11 cases (38 per cent). It usually is described as a symmetrical brownish-tan discoloration which appears on the exposed parts of the body.[5, 6] The skin of the patients appears sallow and they look chronically ill. Pigmentation of the mucous membrane is extremely rare,[5] and was not mentioned in any of our cases. Brownish, wedge-shaped thickenings of the conjunctiva (pingueculae) were noted in nine cases (31 per cent). Lymphadenopathy is not a characteristic of the disease, and only one of our patients exhibited this finding.

Roentgenograms showed evidence of significant skeletal changes in 15 cases (52 per cent); as a rule, the distal ends of the femora were affected. These changes were characterized by thinning of the cortex above the condyles, probably caused by a replacement of the marrow by Gaucher's cells, and the production of the "Erlenmeyer flask deformity" typical of Gaucher's disease. Other bones involved were the tibia, fibula, humerus, radius and the vertebral column. Pathologic fractures were reported in three (10 per cent) of the 29 cases. These fractures occurred in the vertebrae, ribs and hip.

It was of interest that in 24 of the 29 patients (83 per cent) some abnormality, such as anemia, leukopenia or thrombocytopenia, or a combination of these, was indicated by the peripheral blood picture; in the aggregate,

these abnormalities were second in frequency to splenomegaly only. Similar findings have been recorded by many writers.[1, 4-9] By far the commonest finding was anemia,* which was noted in 21 of the 24 cases. The anemia was usually of the hypochromic type and moderate or slight in degree. It was severe (less than 3,000,000 cells per cubic millimeter of blood) in only three instances. The lowest number of cells recorded was 2,666,000 in case 28.

Leukocytes numbered less than 5,000 per cubic millimeter of blood in 13 cases. The lowest value noted was 1,500 in case 3. Leukocytosis was observed in only one case, that of a patient who had multiple nasal boils. The differential count was not remarkable.

Thrombocytopenia with less than 100,000 platelets per cubic millimeter of blood occurred in 13 patients. The lowest count recorded was 16,000 in case 26. Thrombocytosis was not encountered in any patient at the time of initial examination; it did occur after splenectomy, however.

Nine patients showed depression of all three elements in the peripheral blood; seven showed depression of two elements, eight revealed depression of only one element, and five exhibited no depression at all.

Of the 12 patients who complained of easy bruising, eight had thrombocytopenia and four had normal platelet counts. There was slight evidence of increased hemolysis. In some instances the amount of indirect reacting serum bilirubin was elevated or the reticulocyte count was increased, but always in mild degree.

Treatment

Fifteen patients underwent splenectomy, fortuitously dividing the study into two equal groups. Splenectomy was advised mainly because of an uncomfortably enlarging spleen or signs of "hypersplenism." The effects of splenectomy are summarized in table 3. Two patients died in the postoperative period. One, a 12 year old boy (case 15), died two days after splenectomy of shock and acute pulmonary edema. His spleen weighed 1,180 gm. The other, a 52 year old man (case 28), died 36 hours after operation. He had marked hypertension and chronic nephritis in addition to Gaucher's disease. Splenectomy, of course, relieved symptoms of pressure. It also corrected the anemia, leukopenia or thrombocytopenia that existed prior to operation. This apparently was true not only for the immediate postoperative period but also for sustained periods. In only one instance (case 25) were the value for hemoglobin and the number of erythrocytes lower postoperatively (in this case, five years) than preoperatively. In this case, however, the numbers of leukocytes and thrombocytes remained elevated. It is evident that splenectomy effectively corrected the cytopenic state in this disease. Other authors report similar findings.[2, 4, 5, 9-12] Contraindications to splenectomy, where they exist, are principally technical.

*Less than 11 gm. of hemoglobin in the female or 12 gm. in the male, or less than 4,000,000 red blood cells per cubic millimeter of blood in either sex.

TABLE III

Peripheral Blood Findings and Results of Related Tests before and after Splenectomy for Gaucher's Disease: 15 Cases

Case	Date	Hemoglobin, gm.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Platelets, thousands per cu. mm.	Reticulocytes, per cent	BSP test, grade	Serum bilirubin, mg. per 100 c.c.	Roentgenographic Changes; Comments
15 Before splenectomy	4-28-41	10.6	4.82	4.2			1	1.0(I)	Changes in femora characteristic of Gaucher's disease. Spleen: 1,180 gm.
Splenectomy	5-13-41								
After splenectomy	5-15-41	Died of acute pulmonary edema and shock							
16 Before splenectomy	No data available								Marked destruction of necks of both femora. With coxa vara deformity
Splenectomy	12—19	Performed elsewhere; seen 7 years later							
After splenectomy	8-14-26	80%*	4.83	12.1					
17 Before splenectomy	27	5.8	3.57	5.2	76–126	3.5	0	0.8-	Enlargement of medullary portion and thinning of cortex of femora, humeri and radius. Spleen: 324 gm.
Splenectomy	12- 1-27							2.4(I)	
After splenectomy	12- 1-27			11.3–13.4	264–480			0.3(I)	
	7- 5-29	65%*	4.19	16.1	168	2.5			
	7- 9-31	12.7	4.11	13.2					
	12- 2-37	15.5	3.98	15.6					
	3—41	Died							
18 Before splenectomy	10-22-28	65%*	4.14	12.1					Spleen: 1,000 gm. Accessory spleen: 125 gm.
Splenectomy	6- 5-29								
After splenectomy	3- 3-31	12.6	4.02	11.9					
	1-18-50	Died							

* Dare.

TABLE III—*Continued*

Case	Date	Hemoglobin, gm.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Platelets, thousands per cu. mm.	Reticulocytes, per cent	BSP test, grade	Serum bilirubin, mg. per 100 c.c.	Roentgenographic Changes; Comments
19 Before splenectomy	4-15-31	16.9	5.05	5.2-5.4	146	0.3	0	1.8(I)	No evidence of changes in the femur
Splenectomy	31	Performed elsewhere							
After splenectomy	3-11-52	Living; no further data							
20 Before splenectomy	5-18-33	10.5	3.85	3.2–5.0	59	2.6	0	1.4(I)	Osteoporosis, thinning of cortex, and mottling of lower ends of femora. Spleen: 3,433 gm.
Splenectomy	6-13-33								
After splenectomy	6-15-33	13.3	3.55	13.6	100				
	6-17-33	12.9	4.20	11.4	224				
	6-21-33	12.7	4.16	13.4	230				
	6-26-33		4.30	15.2	640				
	6-29-33	13.7	4.04	15.0	400				
	7-10-23	12.6	3.59	8.1					
	10- 9-44		3.84	10.15					
	2- 2-45	Living							
21 Before splenectomy	10- 3-32	12.9	4.04	5.0	81	1	0	1.2(I)	No change evident. Spleen: 600 gm.
Splenectomy	10- 7-32								
After splenectomy	12-17-35	14.9	4.69	9.6	188	1.2	0	1.2(I)	
	7-25-47	Living							

TABLE III—*Continued*

Case	Date	Hemoglobin, gm.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Platelets, thousands per cu. mm.	Reticulocytes, per cent	BSP test, grade	Serum bilirubin, mg. per 100 c.c.	Roentgenographic Changes; Comments
22 Before splenectomy	No data available								No change evident.
Splenectomy	42	Performed in Canada							
After splenectomy	6-26-50	11.6	3.57	12.1	166	1.6	0	0.7(I)	
	2-19-52	11.9	4.40	9.4	169		0	0.5(I)	
23 Before splenectomy	7- 3-47	9.8	3.74	2.7	61		0	0.5(I)	Early changes: flaring of femoral ends and bony striations. Spleen: 1,465 gm.
Splenectomy	7-14-47								
After splenectomy	7-24-47	11.0	4.40	11.9	322–952				
	3-24-52	Living							
24 Before splenectomy	48	11.2	3.97	6.6					Moderate widening of distal femurs, thin cortex. Spleen: 425 gm.
Splenectomy	1-10-49	With removal of accessory spleen							
After splenectomy	1-11-49	9.6	4.24	10.8	177				
	10-28-50	Died							
25 Before splenectomy	45	11.0	3.86	5.6	196	3.4			Changes in femora typical of Gaucher's disease.
Splenectomy	45	Performed elsewhere							
After splenectomy	10-31-50	10.6	3.60	18.6	371	2.2		0.7(I)	
	1-17-51	Living							

TABLE III—*Continued*

Case	Date	Hemoglobin, gm.	Erythrocytes, millions per cu. mm.	Leukocytes, thousands per cu. mm.	Platelets, thousands per cu. mm.	Reticulocytes, per cent	BSP test, grade	Serum bilirubin, mg. per 100 c.c.	Roentgenographic Changes; Comments
26 Before splenectomy	4-29-49	8.0	2.99	3.5	16–38	12.1			No change evident
Splenectomy	6- 9-49	Performed elsewhere							
After splenectomy	7-18-51	10.0	3.29	18.3	"Normal"	3.2			
	4-18-52	Living							
27 Before splenectomy	9-26-35	14.3	3.99	3.3	124	1.7	0	1.2(I)	Spleen: 1,295 gm.
Splenectomy	10- 4-35								
After splenectomy	10- 4-35	14.9	4.15	12.8	222–360	1.8–0.8			
	2-22-52	Living							
28 Before splenectomy	?2	49%*	2.66	2.2	80–240				No change evident.
Splenectomy	8-17-23								
After splenectomy	8-19-23	Died 36 hours after operation							
29 Before splenectomy	5-16-23	11.2	4.46	4.8					No change evident.
Splenectomy	5-22-23								
After splenectomy	6-11-23	75%*	4.33	15.1	112				
	5-24-29	Died							

Other methods of treatment also were used. In some cases roentgen therapy to an enlarged spleen resulted in diminution of the size of the organ, with a consequent partial or complete alleviation of abdominal discomfort. Hematinics were not of value. Transfusions for anemia were given when indicated.

To compare the long-range benefits of splenectomy and conservative therapy, follow-up studies were attempted in all 29 cases. However, in only 21 instances (72 per cent) were we successful. The series is too small to be subjected to statistical analysis, but it is interesting to note that among the 14 patients who did not undergo splenectomy one patient was known to be alive 12 years after his visit to the clinic and two patients were alive 14 years after their visits. Among the 15 patients on whom splenectomy was performed, two were known to be alive 20 years after their visit to the clinic, and one each 16 years, 14 years, 13 years and 11 years after their initial visits.

Summary and Conclusions

The salient clinical features of Gaucher's disease as seen in 29 proved cases have been presented. It was noted that Gaucher's disease is a disease of adults as well as of children and infants. Evidence of hypersplenism was common, and this condition was almost invariably relieved by splenectomy. Follow-up studies showed that six patients who underwent splenectomy were alive 11 to 20 years postoperatively.

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THERAPY OF PULMONARY TUBERCULOSIS WITH SPECIAL REFERENCE TO ANTIMICROBIAL TREATMENT AND RESECTION*

By ELI H. RUBIN, M.D., F.A.C.P., *Bronx, N. Y.*

INCREASINGLY potent weapons are being used against tuberculosis on preventive, diagnostic and therapeutic fronts. Preventive measures stem largely from improved living conditions which enable people to obtain better food and more healthful working hours, and from the adoption of general hygienic measures applicable to all infectious and contagious diseases, including tuberculosis. The results of preventive measures are slow in expressing themselves in tangible form but they are most productive in the long run. This is borne out by the fact that the decline in the death rate from tuberculosis is being shared by people of rising economic standards in spite of minimal advances on diagnostic and therapeutic fronts. Where intensive case-finding campaigns are in progress, tuberculosis is receiving additional setbacks.

Professional workers on the therapeutic front have also done their part. The comparatively modest contribution of physicians, in terms of numbers of patients cured of their tuberculosis as a result of therapeutic measures, is at times magnified through dramatization of minor skirmishes, a form of psychologic warfare which, in a way, also serves a useful purpose. In one respect, however, the physician's rôle is unique: he treats the sick.

Since the physician's part in the fight against tuberculosis concerns the individual, there is obviously no room for standardized treatment. What may be adequate for a middle-aged white male who, after discharge from a hospital, may continue in a sheltered environment, possibly on a pension, may be inadequate for a young Negro or Puerto Rican who, if he does not leave the hospital against advice, is likely to return to a mode of living conducive to an early breakdown and infection of others. Each patient presents a problem in the solution of which many factors have to be considered: age, sex, occupation, economic status, racial susceptibility, the availability of a hospital bed and the various elements which enter into the treatment of the disease itself. The rapid advances being made in the treatment of tuberculosis are creating ever-changing problems. A time-honored modality may become obsolete overnight; one of doubtful value may gain importance as a result of new discoveries. There is nothing static about tuberculosis: "basic" principles are subject to change; even the tu-

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bercle bacillus sooner or later acquires protective armament and has to be attacked on constantly shifting fronts.

Generalizations aside, what is the most pressing problem today, as it concerns the practicing physician, in the therapy of pulmonary tuberculosis? In my opinion it is *timing treatment*. This involves essentially the selective use of bed-rest and graded activities, antimicrobial medication and surgery, especially resection. What is generally known as the "rest cure" remains the sine qua non of treatment for the reason that it takes a long time for caseous foci and cavities to heal even if they can become sterilized. Timing treatment also takes into consideration the proper choice of a place where the patient can be treated most effectively, including hospital, home, clinic or physician's office.[1]

Antimicrobial Treatment of Tuberculosis

Shortly after the inclusion of streptomycin in the armamentarium against tuberculosis, we had occasion to write: "Streptomycin may be found most effective if used in the manner of therapeutic pneumothorax. Both forms of treatment are essentially suppressive; one exerts its effects mechanically, the other biotically. Both aid natural processes of healing. In the treatment of advanced pulmonary tuberculosis, associated with fever, cough and expectoration, when there is imminent danger of canalicular spread of infection, relatively large doses of streptomycin (2 gm. daily in divided doses) might be used until there is some degree of stabilization of the disease. Less acutely progressive tuberculosis may require 1 gm. daily. The dose of streptomycin might shortly be cut to 0.5 or 1 gm., administered two or three times a week, to maintain a sustained suppressive effect of the antibiotic in the body until the disease shows a decided tendency to regress roentgenologically. The total dosage could be kept within 150 gm., well within toxic limits and possibly within the period in which most of the organisms acquire resistance. If the disease is amenable to collapse or other surgical measures, and if there is need to fortify the patient with streptomycin because of undue operative risks, the antibiotic should be administered for a short time prior to such contemplated operations and for a time thereafter.

"In the present state of knowledge of the value and limitations of streptomycin, it is inadvisable to use the agent as a short-cut in the treatment of pulmonary tuberculosis or, for that matter, as a routine method of treatment under any circumstance. As long as there is a reasonable expectation of obtaining arrest of the disease on a modern sanatorium regimen, streptomycin should be reserved for special indications." [2]

When para-aminosalicylic acid (PAS) became available it was found that smaller doses of streptomycin could be used over longer periods, with commensurably less danger that the tubercle bacillus would become resistant to the medication. Currently a schedule of streptomycin or dihydrostreptomycin in 1 gm. doses, two or three times a week, plus 10 to 12 gm. PAS

daily, is being used generally in the United States, except during the initial acute febrile stages of the disease, when the antibiotic is given daily. This plan of treatment fulfills a major prerequisite of antibacterial treatment of tuberculosis: prolonged suppression of the tubercle bacillus, thereby enabling natural processes of healing to come to the fore. Under suitable conditions, healing continues long after the antimicrobial medication has exhausted its potency or has been discontinued.

We are at a cycle in the treatment of tuberculosis when another prerequisite may be fulfilled: the establishment of an additional line of defense. That a reserve agent is urgently needed is attested by the many patients who have had prolonged periods of hospitalization, including collapsing measures, repeated courses of antibacterial medication, and surgical and other forms of treatment, and whose disease is still active and progressive. In the months to come increasing numbers of patients will undoubtedly be occupying hospital beds who have had, in addition, isoniazid and, in time, possibly other antibacterial agents. Judicious use of the various modalities of treatment now available should help keep the number of patients with irreparable destructive changes in the lungs to a minimum.

When streptomycin and PAS were the sole antibacterial agents available it was almost impossible to withhold these agents, even from patients who might have got along without them. The pressure on the physician was too great. Today, with an additional potent agent, isoniazid, at hand, the physician has more freedom of action. In the light of past experience it would seem best, until additional potent nontoxic agents become available, that an effort be made to keep isoniazid in reserve for special contingencies. The reason for suggesting this plan of treatment is based on recent studies on the hydrazides in a large number of patients at Seton and Morrisania City Hospitals.[8]

The comparative efficacy of isoniazid alone, isoniazid plus dihydrostreptomycin, isoniazid following dihydrostreptomycin-PAS, and dihydrostreptomycin-PAS, was studied in 258 patients with pulmonary tuberculosis and its complications. The greatest degrees of improvement were noted in patients with predominantly acute disease in the several categories mentioned. In the order of relative effectiveness, judged by the degree of roentgenologic clearing at the end of four months, the best results were obtained in patients who received isoniazid, especially in the group treated with isoniazid plus dihydrostreptomycin. Patients with predominantly acute disease who received isoniazid after having had dihydrostreptomycin-PAS and those who received dihydrostreptomycin-PAS gave comparable results. Maximal benefits of isoniazid alone were obtained in the majority by the end of the fourth month. After six months there was beginning evidence of deterioration in several.

There is no doubt that isoniazid is a powerful but relatively short-acting antituberculosis agent. When the drug is administered alone the tubercle bacillus acquires resistance quite rapidly. This was recently shown in a

series of sensitivity tests reported by the Medical Research Council of Great Britain.[4] Drug-resistant tubercle bacilli were obtained in 62 per cent of positive cultures after three months' treatment with isoniazid alone. When streptomycin was added, isoniazid-resistant bacilli were obtained in only 13 per cent of positive cultures at the end of three months. The appearance of resistance in vitro is not a laboratory phenomenon but reflects the ability of the tubercle bacillus to react against the drug in the human body. An earlier communication by the Research Council showed that 28 per cent of the cases with resistant organisms revealed radiologic improvement, as compared to 62 per cent of those not known to have become resistant.[5]

Although isoniazid plus dihydrostreptomycin gives the best immediate results, due to a synergistic action of the two, this per se should not be the reason for the simultaneous use of both agents. Granting that bacillary resistance is significantly delayed by the combined use of isoniazid and dihydrostreptomycin, it would still be injudicious to use two potent agents in moderately advanced disease when one usually suffices as far as bacteriostasis is concerned, or to exhaust both agents in far advanced disease when there is little prospect of cure with antibacterial medication alone.*

Until more is known, it is suggested that dihydrostreptomycin-PAS be used in the routine antibacterial treatment of tuberculosis, and that isoniazid be held in reserve for special occasions. The latter will be found in patients who do not tolerate PAS or in those with high fever, excessive cough and expectoration or marked loss of weight, in the presence of tuberculous complications, or in patients of susceptible groups such as Negroes, Puerto Ricans and American Indians, who do not respond satisfactorily to conventional treatment. Under such and similar conditions isoniazid, 300 to 400 mg. daily, can be added to dihydrostreptomycin-PAS until the desired effect is obtained. In patients with pulmonary tuberculosis in whom there is strong likelihood that surgery may be necessary (and such patients are increasing in number), it is of the utmost importance to keep isoniazid in reserve. In a number of our patients who had had surgical treatment and who later sustained reactivation of the disease, isoniazid was a life-saving measure. While we do not as yet have scientific data on the effects of giving isoniazid in the manner suggested, the plan proposed does not seem illogical.

If the tubercle bacilli are resistant to streptomycin, or the patient is sensitive to the antibiotic, isoniazid may be given with PAS on the principle that combined chemotherapy delays the emergence of resistant organisms. There is some evidence that the combination of isoniazid and PAS may be synergistic, occupying a position close if not equal to that of isoniazid plus streptomycin.[6] As yet, too few patients have been followed on combined isoniazid and PAS medication to warrant conclusive statements at this time. But there is practically unanimous opinion to the effect that isoniazid should not be given alone.

* Recent studies indicate that a combination of equal parts of streptomycin and dihydrostreptomycin is least toxic.

The reasons for suggesting that isoniazid rather than streptomycin be kept as a reserve agent stems from the fact that, although isoniazid gives excellent results in acute pneumonic tuberculosis, the drug is also able to diffuse into dense caseous and necrotic lesions in high concentrations, especially in the lungs, and possibly more readily than streptomycin.[7] It would seem desirable, therefore, to withhold the more diffusable agent as a second line of defense. Undoubtedly occasions will arise when it will be preferable to use isoniazid plus streptomycin plus PAS relatively early in the course of the disease, in the hope that the process will respond to antibacterial treatment alone. It is questionable, however, if this should be done as a routine method of treatment in the present state of knowledge.

Against the use of streptomycin plus isoniazid as the mainstay in the treatment of tuberculosis (unless the patient cannot tolerate PAS) is the fact that giving a combination of two drugs to a patient whose organisms are resistant to one of the two is tantamount to giving the other alone.[4] Under such conditions the patient might become resistant to the two most potent drugs now available relatively early in the course of the disease and be left vulnerable to later reactivations. From a practical standpoint, it would seem preferable to place the patient in an institution and to subject the patient relatively early in the course of treatment to the inconvenience incident to intramuscular streptomycin and oral PAS. The patient can be kept under closer supervision during this period. Furthermore, in the hands of the inexperienced the combination of isoniazid and PAS lends itself more readily to abuse as a "therapeutic test" of undiagnosed pulmonary disease and may be used as a substitute for more definitive treatment.

Should isoniazid and PAS be indicated without streptomycin, it would be desirable to combine the drugs in a single capsule or tablet. Patients not sufficiently indoctrinated in the "rest cure" in a well conducted sanatorium are apt to dispense with the more objectionable PAS and take isoniazid alone. The final word on the subject has not been written. The addition of new antibacterial agents might change the picture overnight. For the time being it would seem that the potential value of combining isoniazid with streptomycin and PAS in the average case of pulmonary tuberculosis is not sufficiently documented to warrant the use of isoniazid as a routine measure. As aptly stated in a recent editorial in the *British Medical Journal:* [8] "When patients are desperately ill, it is reasonable to give them all three drugs in the first place, but again it may be advisable to withdraw isoniazid into reserve as soon as the most acute phase has been controlled. If, because of resistance to streptomycin and PAS, the patient has to receive isoniazid, which has been kept in reserve, its use should be carefully timed to cover a crisis. The last important chemotherapeutic reserve must not be frittered away."

The initial reports on the hydrazides by the Seaview Hospital group of investigators [9] concerned chiefly iproniazid. The results were very impressive in spite of the toxic manifestations, which the authors duly noted.

Our experience with iproniazid in 49 cases at Seton Hospital leads us to conclude that, although the drug is a potent antituberculosis agent, in several respects possibly superior to isoniazid, the toxic and side reactions encountered are of a frequency and severity to preclude the routine use of the drug at the present time. In approximately half of the patients iproniazid had to be discontinued prematurely because of the development of severe dizziness, drowsiness, muscle twitchings, blurred vision, deafness, constipation, increasing anemia, liver damage and, in one instance, frank psychosis.

Resection in Pulmonary Tuberculosis

The treatment of pulmonary tuberculosis by measures applied to the diseased lung directly has undergone a radical change. Collapsing procedures such as pneumothorax and thoracoplasty are being used less and less, the latter more often to supplement resection rather than as an independent operation. Resection, on the other hand, is being employed on a larger scale. One hears the almost plaintive cry, "There is still a place for pneumothorax," but it is becoming increasingly difficult to find a patient presenting the necessary indications. In 1950, pneumothorax was induced or attempted at Seton Hospital in 33 patients; in 1951, in 27; in 1952, in four. In the first five months of 1953, pneumothorax has not been induced or attempted in a single instance; in fact, at present there are no patients in the hospital or clinic receiving pneumothorax inflations. Pneumoperitoneum has apparently also seen its heyday, as prognosticated by Amberson,[10] who anticipated a more discriminating use of this form of treatment with the increased use of specific drugs. In 1950 pneumoperitoneum was induced at Seton Hospital in 72 patients; in 1951, in 54; in 1952, in 35, and in the first five months of 1953, in four. The intensive use of the hydrazides in 1952–1953 was undoubtedly responsible in part for the somewhat precipitous decline in the use of collapsing procedures at Seton Hospital. However, they were not withheld intentionally; rather, it seemed preferable to use bed-rest and prolonged antibacterial medication until such time as local measures could be applied.

When resectional surgery was introduced it was applied to the most difficult types of tuberculosis, disease not suited for pneumothorax or thoracoplasty, disease complicated by tuberculous bronchitis or bronchiectasis, encapsulated empyemas and cavities remaining after ineffective thoracoplasties. Only after undergoing severe tests of this nature was resection adopted as a measure in its own right. The enlargement of indications to include newly discovered cases paralleled, on the one hand, the experience being acquired by surgeons with the operation and, on the other, the decreasing numbers of patients with complicated pneumothoraces, nonexpanded lungs, empyemas and ineffective thoracoplasties requiring "patching up." The value of resection is now recognized; it is the preferred method of surgical treatment of pulmonary tuberculosis in nearly all institutions hav-

ing the services of trained thoracic surgeons. But the applicability of resection to the several forms of the disease is still being explored.

From an experience with more than 200 patients with pulmonary tuberculosis treated with resection, including a sizable number of children and adolescents and many poor risks in tuberculosis-vulnerable groups, the tendency at Seton Hospital has been to widen rather than to restrict its use.[11] It should be emphasized, however, that a prolonged period of bed-rest and antibacterial medication has to be applied before and after operation, especially in patients with initially widespread disease, to allow time for caseous foci in the nonresectable portions of the lungs to undergo as complete healing as possible. Resection of the major focus of disease does not shorten the time of healing of caseous foci in the remaining lung, and we know only too well how much diseased tissue is left after the major focus is removed.

A detailed discussion of resectional surgery is beyond the scope of this presentation. Suffice it to mention that the indications and contraindications of the operation are often dictated by the capacity of the lungs to compensate functionally for the parts removed, a vital consideration in patients of older age groups. In younger patients the use of resection is dictated not only by the type and extent of the disease but also by prognostic implications associated with tuberculosis, even of limited extent, in certain age and racial groups. That months or years after a technically successful operation a patient may suffer relapse does not necessarily reflect poor judgment on the part of the physician or lack of skill on the part of the surgeon. The aim of resectional surgery is to remove grossly destroyed portions of the lung which are potentially dangerous to the patient. The removal of such diseased tissue helps the patient to weather a critical period; it does not alter the patient's innate susceptibility to subsequent reactivation of latent foci or to the development of new foci. Of prime importance, as mentioned previously, is the timing of medical and surgical procedures so that one supplements the other.

Timing Treatment in Tuberculosis

The treatment of active pulmonary tuberculosis is bed-rest fortified by antimicrobial medication, primarily dihydrostreptomycin and PAS. Isoniazid is indicated, in our opinion, as a "booster" under conditions mentioned previously. As soon as the disease shows evidence of becoming quiescent and localized to a portion of a lung, resection comes into consideration. This may take months or years, or may never be realized. Thoracoplasty is occasionally indicated in patients in whom resection cannot be done. More often, thoracoplasty is used in conjunction with lobectomy to prevent undue overdistention of the remaining lung or to reduce the size of a hemithorax following pneumonectomy.

A patient with active, predominantly fibrotic disease of limited extent can be managed quite expeditiously. The patient is placed on a rest regi-

men and given dihydrostreptomycin-PAS. When symptoms and serial x-rays show that the process has become stabilized, resection comes into consideration. The preoperative preparation may be a matter of three or four months, or even less, if one is dealing with a circumscribed process, as is often the case when the disease is discovered accidentally in individuals in their late twenties or thirties. After operation the patient requires a prolonged period of convalescence, including antibacterial medication, to insure inactivity of remaining foci. This can be carried out partly in the hospital, partly at home, depending on the facilities available.

Between the two extremes of the finding of a localized indolent process amenable to resection early, and advanced pulmonary tuberculosis requiring several years of rest and antibacterial treatment before surgery can even be contemplated, there is a wide field where judgment is required as to the timing of specific measures. There is no set formula for the application of therapeutic agents, for the reason that in tuberculosis one is dealing not only with a pulmonary disease but also with an individual in whom many factors have to be considered, including the relative prognosis of tuberculosis in different racial groups, the patient's occupation, economic status, home conditions and the various elements which make tuberculosis a socio-economic as well as a clinical problem. Last but not least, one has to be prepared to change one's opinion at short notice. What is the preferred method of treatment today may be outmoded tomorrow.

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TRAUMA AND PREËXISTING DISEASE WITH RUPTURE OF SPLEEN *

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DOES "spontaneous" rupture of the spleen usually occur in a normal organ? Can the spleen be involved in a disease process that might be obscured by the crisis brought about by rupture? The answers given to these questions are not entirely satisfactory. There are several good reasons for these uncertainties:

1. Several systemic diseases that involve the spleen are frequently not accompanied by symptoms which compel the affected individual to consult a physician; if the patient does see a physician the disorder may remain undiagnosed because of a lack of outstanding symptoms. After splenic rupture precipitates a surgical emergency, the underlying disease may be overlooked, or disappear after splenectomy.

2. The surgically removed spleen is often fragmented and contains clotted blood. Since the true weight of the organ before rupture is unknown, enlargement is often attributed to the changes occurring after rupture. Histologic examination for what seems to be a clear-cut clinical diagnosis is often perfunctory, and, moreover, the spleen does not lend itself to specific histologic diagnosis in many diseases.

3. The concept that a ruptured spleen should be suspected of previous disease does not seem widely established.

Spontaneous or traumatic rupture of the spleen has been described in association with pregnancy,[1] congenital anomalies of the organ,[2] congestive splenomegaly,[3] Gaucher's disease,[4] chronic and acute leukemia,[5, 6] hemangioma,[7] and a number of infections (acute sepsis,[3] infectious mononucleosis,[8] infectious hepatitis,[9] chronic malaria,[3] typhoid fever,[3] sarcoidosis,[10] and tuberculosis [3]). No previous mention has been found, however, of the association of rupture with congenital hemolytic jaundice.

CASE REPORTS

Case 1. A 49 year old white milkman was admitted to the Fitzgerald-Mercy hospital on July 3, 1948. He had been in good health until two days before when, delivering milk, he fell and to protect his fountain pen threw his left arm across his chest. He landed on his left side in such a manner that his left elbow was driven forcibly against the upper left quadrant of the abdomen. Immediately after, he experienced severe dyspnea and pain in both sides of the chest. He went to bed and the dyspnea gradually disappeared. The next day he complained of pain in the left upper quadrant of the abdomen and on the following day was admitted to the hospital.

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In the history obtained on admission the patient denied any knowledge of previous diseases and gave a negative family history. He was thin and apprehensive, and while being examined seemed to have moderately severe pain. The blood pressure was 120/80 mm. of Hg; temperature, 100° F.; pulse rate, 112 per minute; respirations, 28 per minute. There were diffuse tenderness, rigidity and flatness to percussion over the left upper abdominal quadrant. The blood count showed 8.0 gm. of hemoglobin with 2,210,000 erythrocytes and 15,000 leukocytes, with a moderate shift to the left. The urinalysis was negative. The day following admission the patient was jaundiced, and the serum bilirubin was found to be 3.9 mg. per 100 c.c., with a negative direct van den Bergh reaction. During the next week the tenderness gradually abated, and by July 12 a poorly defined mass was felt in the left upper abdominal quadrant. The roentgenogram showed extrinsic pressure on the stomach, transverse colon and splenic flexure. During this time the temperature had risen to 100° F. daily, with a pulse rate of 100 per minute. On July 15 a detailed history obtained from the patient's wife disclosed that in 1922 the patient had had jaundice for three weeks which did not require his stopping work. In 1926 he had had pneumonia, and jaundice was noted. The patient's parents, according to his wife, had always been well, but the patient's one sibling, a brother, had had his spleen removed five years before, at another hospital.

A further inquiry into the history of the patient's brother revealed that he had been admitted to the Hospital of the University of Pennsylvania on April 2, 1945, because of large ulcerations of both ankles and occasional jaundice since childhood. He had an enlarged spleen, the diagnosis of congenital hemolytic anemia had been made, and the spleen was removed. There was rapid and complete recovery. The spleen weighed 2,300 gm. and on histologic examination showed many siderofibrotic nodules.

By July 15 the patient was slightly icteric, and a large mass was palpable in the left upper abdominal quadrant. The blood count at this time showed 9.0 gm. of hemoglobin, 2,870,000 erythrocytes and 8,000 leukocytes, with a normal differential count. He had received three 500 c.c. transfusions of blood since admission. The stained smear showed a large proportion of spherocytes among the erythrocytes. A diagnosis of ruptured spleen in a patient suffering from congenital hemolytic jaundice was made. A splenectomy was performed on July 19. The spleen was large and adherent to the stomach, omentum and diaphragm. As the adhesions were separated along the superior pole, dark, reddish brown liquid was found between the spleen and diaphragm.

Pathologic Examination: The spleen weighed 987 gm. The capsule was torn in several places, and large areas of clotted blood were present. Two thirds of the surface showed a subcapsular hemorrhage. The cut surface was dark red. Two infarcts were present, each 3 cm. in diameter. Histologic examination showed slight hemosiderosis and extravasation of blood into the pulp. Findings pathognomonic of hemolytic disease were not present. The histologic slides were shown to several pathologists without appraising them of the clinical history, and none could diagnose the nature of the disease or even state definitely that the spleen was diseased.

The patient made an uneventful recovery. A follow-up examination on October 25, showed the following: hemoglobin, 12.0 gm.; erythrocytes, 3,990,000; leukocytes, 11,200; platelets, 632,000. Differential count: neutrophils, 70 per cent; eosinophils, 2 per cent; basophils, 3 per cent; lymphocytes, 16 per cent; monocytes, 4 per cent; and disintegrated, 5 per cent. Erythrocyte fragility test in hypotonic saline solution: hemolysis beginning before 0.60 per cent and complete at 0.40 per cent (control, 0.46 per cent to 0.34 per cent). The stained smear contained many spherocytes.

There were numerous clues to the true state of affairs in this patient, but many were not easily attainable and others not easily interpreted. A review

of the record illustrates how preëxisting disease may be obscured after rupture of the spleen has occurred:

1. The patient, suffering from severe pain, did not remember that "his eyes had been yellow" 26 years before, or that his brother had had a splenectomy.

2. The icterus found on admission could be explained as due to absorption of hemolysed blood from the intra-abdominal hemorrhage. The size of the spleen could be due to hematomata and extravasated blood.

3. The anemia was obviously attributable to the intra-abdominal bleeding. It was only after more probing into the patient's history that the clues in the past and family history were obtained. The demonstration of spherocytes and an increased erythrocyte fragility in hypotonic saline solution then established the diagnosis.

Is the spleen of hemolytic disease prone to rupture after mild trauma? A splenectomy was observed in an 18 year old boy with congenital hemolytic jaundice. The spleen was enlarged to approximately four times the normal size and was smooth and free of adhesions. As the surgeon delivered the spleen the slight trauma caused a subcapsular hematoma which grew rapidly and attained a diameter of 8 by 6 cm. (figure 1). This was actually a thin-walled sac of blood and would undoubtedly have ruptured with slight additional trauma. This may indicate that the spleen of congenital hemolytic disease is not particularly resistant to trauma.

This experience led to a consideration of other diseases accompanied by an enlarged spleen that may not have sufficient clinical manifestations to cause the individual to see a physician.

Case 2. A 42 year old white man was admitted to the Pennsylvania Hospital on July 17, 1941. One year before admission he had injured the lower part of his chest in a fall. Since that time he had experienced a peculiar sensation in the left upper part of his abdomen. Five weeks before admission he fell from a scaffolding four feet above the ground. One week before admission he noticed pain in the left shoulder and on the day of admission there was abdominal pain with nausea.

On admission his blood pressure was 78/58 mm. of Hg; pulse rate, 120 per minute; respirations, 28 per minute; temperature, 101° F. The patient was pale and in extreme pain, and the extremities were cold. The entire abdomen was tender and rigid. Peristalsis was hypoactive. The leukocyte count was 300,000. All stages of the neutrophilic granulocytic series were present, with many eosinophils and basophils. Erythrocytes numbered 2,500,000; platelets were abundant. The cellular distribution of the sternal marrow was that of chronic myeloid leukemia.

The day after admission the patient was operated upon and a large ruptured spleen removed. The patient did poorly and died on the tenth postoperative day. Autopsy confirmed the diagnosis of chronic myeloid leukemia.

The following diseases are characterized by splenomegaly, but the diagnosis both clinically and pathologically may be difficult.

Infectious Mononucleosis: This disease may simulate a mild respiratory infection or may even be almost symptom-free, and yet splenomegaly may be marked. Recently, one of the residents at the Pennsylvania Hospital ex-

FIG. 1. Gross appearance of spleen removed from a patient with congenital hemolytic icterus. Note the large hemorrhagic bleb at one of the poles. Before the spleen was handled the surface was normal.

perienced slight malaise and noticed that he had a few enlarged cervical lymph nodes, and in pursuing this observation he discovered that he had a spleen easily palpable 3 cm. below the costal margin. Infectious mononucleosis was confirmed by examination of the blood and a strongly positive heterophil antibody test. He doubted if any lay person with such slight symptoms would have consulted a doctor. During this time he was obviously liable to splenic rupture from mild trauma. That trauma even as mild as palpation may rupture the spleen in this disease is brought out by the report of Smith and Custer.[8]

Acute Hepatitis: That homologous serum hepatitis and infectious epidemic hepatitis may be mild diseases, not accompanied by jaundice, is generally known. It is perhaps not so widely appreciated that even the disease with slight symptoms may be accompanied by an appreciable enlargement of the spleen [11] which is susceptible to rupture.[9]

Idiopathic thrombocytopenic purpura and splenic neutropenia or pancytopenia are conditions that may have mild manifestations and usually slight to moderate splenomegaly. No reports of splenic rupture complicating these diseases have been encountered.

DISCUSSION

It is difficult to understand why a normal spleen should rupture, either spontaneously or with mild trauma. It is easier to visualize that a moderately enlarged spleen from a mild systemic disease may rupture after undergoing mild trauma the time and circumstances of which may not be remembered.

Hepatitis and infectious mononucleosis may be overlooked clinically, and histologic examination of the spleens in these diseases, unless done with especial care, may not disclose any significant changes.

In the case of congenital hemolytic disease, thrombocytopenic purpura and splenic neutropenia, splenectomy is usually curative and would further mask the predisposing cause to splenic rupture.

Summary and Conclusions

1. When a spleen undergoes spontaneous rupture or ruptures after mild trauma a search for a predisposing cause is indicated.

2. Diseases predisposing to rupture of the spleen may be divided into two categories: (a) diseases easily diagnosed by examination of the patient and the removed spleen—leukemia, Gaucher's disease, malaria, sarcoidosis, tuberculosis and acute sepsis; (b) diseases in which the diagnosis may be occult because of a lack of clinical manifestations and of a specific histologic pattern in the spleen—infectious mononucleosis, virus hepatitis and congenital hemolytic disease.

3. Rupture of two diseased spleens is reported, one in a patient with chronic myeloid leukemia, the other in a patient with congenital hemolytic anemia. Neither of these patients was aware of preëxisting disease before rupture of the spleen occurred.

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THE USE OF DEMEROL IN PATIENTS WITH BRONCHIAL ASTHMA *

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Soon after the discovery of a new group of analgesic compounds in 1939,[1] one of these, 1-methyl-4-phenyl-piperidine-4-carboxylic acid ethyl ester hydrochloride, was intensively investigated. This drug is generally known under the name of Demerol, meperidine, Dolantin, Pethidine or Isonipecaine, and its chemical structure is shown in figure 1.

Pharmacologic investigations showed that Demerol has a weak atropine-like and a stronger papaverine-like action on smooth muscle [2]; these actions were demonstrable on spastic or stimulated smooth muscle. Schaumann [1, 3] also demonstrated spasmolytic action on intestinal or bronchial smooth muscle whether contraction was caused by a cholinergic drug, by nerve stimulation or by a musculotropic agent such as histamine or barium ions.

Animal experiments by Duguid et al.[4] and others [5, 6] demonstrated Demerol to be an effective antihistaminic agent. In man, Curry et al.[7] observed that Demerol in doses of from 50 to 100 mg. given intramuscularly or by nebulization "afforded from moderate to complete protection" against the effects of intramuscular methacholine given to asthmatic subjects.

The analgesic value and relative safety of Demerol were corroborated by experimental and clinical investigations. Many investigators commented on the fact that they observed little or no respiratory depression. Roby and Schumann [8] and others [9, 10] recommended its use in obstetrics because of good analgesia without simultaneous induction of significant degrees of respiratory depression in the newborn. In addition, many favorable clinical reports have appeared on the use of Demerol in patients with bronchial asthma. James et al.[11] recommended its use in preoperative and postoperative medication of patients with bronchial asthma. Yonkman [12] reported on four cases in status asthmaticus who were not relieved by Adrenalin, aminophylline, rectal ether, etc.; three of these responded well to Demerol. Curry [7] found that Demerol, 50 to 100 mg. given every two to three hours, could be used in acute paroxysms of bronchial asthma, that it rarely caused depression of respiration, and that the sputum might become slightly viscid. Barach [14] reported on the use of Demerol for one or more days to overcome aminophylline or epinephrine fastness of patients with pulmonary emphysema and bronchial asthma. He found no respiratory

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depression. Similarly, other observers reported favorably on the use of Demerol for the treatment of bronchial asthma.[16, 20]

However, some unfavorable reports on the use of Demerol can be found. Rackemann [21] feels that Demerol and all related drugs should never be used in bronchial asthma. Rowe [22, 23] likewise states that it is contraindicated especially in intractable asthma, and similar statements are made by others.[24, 25, 26] The only absolute contraindication to Demerol, it seems, is the presence of intracranial lesions.[27] While only *large* doses of Demerol will depress respiration, apparently by central action, a clinical dose may cause such depression in a patient with intracranial lesions, as reported by Guttman.[27] Experimental studies in dogs by Gruber et al.[5] showed that 2 mg. per kilogram given intravenously will cause a sudden decrease in depth and rate

DEMEROL HYDROCHLORIDE

(MEPERIDINE)

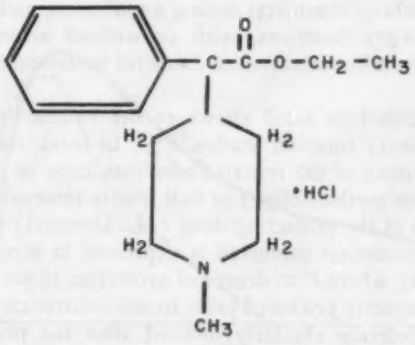

FIG. 1. Structural formula of Demerol Hydrochloride.

of respiration, which returns to normal. Repeat doses caused irregular rhythm and cessation of respiration in the expiratory phase. Much larger doses resulted in apnea and death of the animal. Observation in mice and rabbits by Way [28] showed little sedative effect or depressant action when given in therapeutic doses, but large doses of Demerol provoked diffuse excitation, manifested by tremors, jerking movements and, finally, convulsions. The cortical effects of large doses of Demerol in man were investigated by Andrews,[29] who gave as much as 3.18 gm. in 24 hours to men formerly addicted to morphine. They exhibited nervousness, disorientation, tremors and jerking movements of the extremities.

The side effects of Demerol are many and varied, and may be seen with a small dose as well as a large dose. They may vary from dizziness, anorexia, nausea and vomiting to flushing, perspiration, dryness of mouth

or grogginess and sleep. Addiction to Demerol, when it is used over a prolonged period of time, can of course occur.[26]

The fate of Demerol was investigated by several: Lehman et al.[80] found that about 10 per cent escapes destruction and is excreted in the urine, regardless of the size of the dose or the presence of tolerance. Way et al.[81] reported that the highest tissue concentrations were found in order in the lungs, liver, kidney and spleen. They felt that Demerol is probably destroyed by an esterase which is found only in the liver.

Because of the frequent use of Demerol in patients with bronchial asthma, and the scarcity of experimental and laboratory observations on the effects of Demerol on the respiratory mechanisms, we undertook to study the effects of a clinical dose administered to patients with chronic bronchial asthma.

Methods

Our studies consisted of (1) protection studies with Demerol against the bronchoconstrictor effects of intravenously administered histamine or methacholine in asthmatic subjects during a remission, and (2) observations on various pulmonary functions, with or without arterial blood studies, before and after the administration of Demerol to asthmatic patients during an acute attack.

We have described in detail elsewhere the technic of performing protection and pulmonary function studies.[32, 33] In brief, the method for protection studies consists of the repeated administration of the bronchospastic agent (histamine or methacholine) at half hourly intervals, before and after the administration of the protecting drug (i.e., Demerol) to be tested. The measurement of protection conferred is expressed in terms of the equation $P = C\text{-}E/C \times 100$, where $P =$ degree of protection in per cent, $C =$ control decrease in vital capacity produced prior to administration of the therapeutic agent, and $E =$ decrease similarly induced after the protecting drug has been given.

Pulmonary Function Studies: Several or all of the following observations were carried out on each patient: the resting minute ventilation, respiratory rate, tidal volume, vital capacity, maximal breathing capacity, and arterial blood analysis for oxygen and carbon dioxide content and capacity, pH, chlorides and hematocrit. These observations were made before and at time intervals after the subcutaneous administration of 50 to 100 mg. Demerol. The respiratory rate, tidal volume and vital capacity were obtained by the direct spirographic method. The resting minute ventilation was calculated by multiplication of the tidal volume and respiratory rate. The maximal breathing capacity was performed with a low-resistance Rudolph valve, and the expired air collected in a Douglas bag which was then measured with a gas meter.

The arterial blood oxygen and carbon dioxide were determined by the Van Slyke methods and the pH on a Cambridge meter.

Case Material

The patients used in this study had chronic bronchial asthma. Most of them were known to our laboratory and had been subjects for various studies related to bronchial asthma over several years.

Results

I. Protection Studies: Demerol, 100 mg., was given intramuscularly in an attempt to protect against the bronchoconstrictive effects of intravenous histamine (six subjects) and intravenous methacholine (five subjects).

The average results are graphically presented in figure 2, which demonstrates a maximal protection of 60 per cent against histamine which was

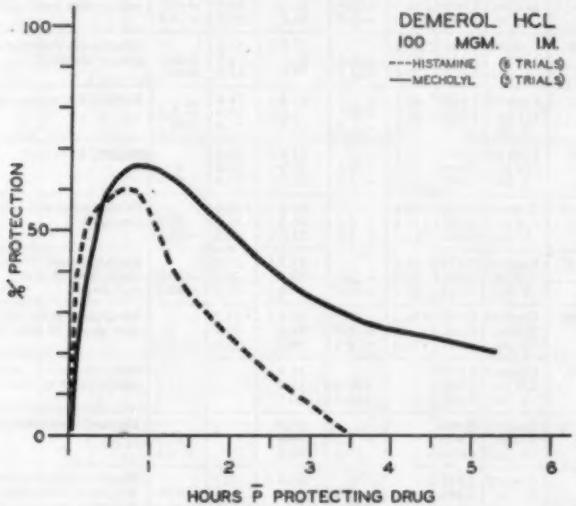

Fig. 2. Protection afforded by intramuscular administration of Demerol Hydrochloride against dyspnea and bronchoconstriction induced by intravenous histamine and methacholine in asthmatic patients.

obtained in about 45 minutes. "Significant" protection, i.e., greater than 40 per cent, was demonstrable for an average of 80 minutes. Against methacholine, the maximal average protection of 66 per cent was obtained in 50 minues and "significant" protection was observed for an average of 140 minutes.

In man, therefore, Demerol appears to be a fairly good antihistaminic agent and a very good anticholinergic agent.

II. Pulmonary Function Studies: Subjectively, all patients felt slightly to greatly relieved and "eased" after the injection of Demerol.

The objective results were as follows:

1. Vital Capacity: The vital capacity increased in 12 and decreased in two instances one-half hour after the injection, while after one hour it was still increased in eight and was below the control value in five instances (table 1). The greatest increase of the vital capacity recorded was 55.6

TABLE I

Changes in Pulmonary Function after Single Injection of Demerol (subcutaneously) during Acute Attack of Bronchial Asthma

Patient; Sex; Age; Body Surf. (m^2)	Time	V.C. (L.)	% of Pred.	% Change	M.B.C. (L./min.)	% of Pred.	% Change	Comments
1; F; 37; 1.64	Control	1.426	73.0		28.9	32.8		Very dizzy but feeling less dyspneic after injection.
	1/2 hr.	1.305	60.0	− 8.5	—	—		
	1 hr.	1.270	46.4	−10.9	26.0	29.5	−10.0	
2; F; 37; 1.77	Control	2.635	91.0		52.0	52.7		1/2 hr. after injection less wheezing and feeling more comfortable.
	1/2 hr.	2.949	102.0	+11.9	68.2	69.0	+31.2	
	1 hr.	2.949	102.0	+11.9	51.5	52.0	− 0.9	
3; F; 27; 1.40	Control	1.386	59.0		42.6	52.0		Progressive decrease of wheezing and greater comfort.
	1/2 hr.	2.156	80.0	+55.6	61.0	74.5	+43.2	
	1 hr.	2.013	70.4	+45.2	70.0	85.5	+64.3	
4; F; 29; 1.62	Control	1.412	66.1		20.3	21.8		Slightly less wheeze and more relaxed.
	1/2 hr.	1.554	81.7	+10.1	18.6	19.9	− 8.4	
	1 hr.	1.159	57.5	−17.9	16.2	17.4	−20.2	
5; F; 29; 1.62	Control	1.967	66.5		25.9	27.8		Slightly improved.
	1/2 hr.	2.344	79.2	+19.2	25.9	27.8	0	
	1 hr.	1.861	62.9	− 5.4	25.9	27.8	0	
6; M; 52; 1.65	Control	4.020	143.1		87.4	118.6		Feeling more relaxed and more comfortable.
	1/2 hr.	4.283	152.4	+ 6.5	68.3	92.6	−21.8	
	1 hr.	4.348	154.7	+ 8.0	71.0	96.3	−18.8	
7; F; 22; 1.52	Control	1.371	44.4		27.7	27.9		Feeling better; 10 min. later became dizzy and drowsy. Chest findings unchanged.
	1/2 hr.	1.416	45.8	+ 3.3	19.4	20.9	−30.0	
	1 hr.	1.814	58.7	+32.3	16.6	17.9	−40.0	
8; M; 29; 1.84	Control	4.734	119.5		97.4	74.2		Breathing better and more comfortable about 10 min. after injection.
	1/2 hr.	4.920	124.2	+ 3.9	91.8	69.9	− 5.7	
	1 hr.	4.541	114.6	− 4.1	94.6	72.0	− 2.9	
9; F; 23; 1.75	Control	1.793			24.9			Felt improved temporarily. Uncomfortable at the end of an hour.
	1/2 hr.	2.700		+50.6	31.8		+27.7	
	1 hr.	2.480		+38.3	30.4		+22.1	
10; M; 25; 1.70	Control	4.986			47.3			Marked improvement.
	1/2 hr.	4.675		− 6.2	58.4		+23.5	
	1 hr.	4.100		−17.8	47.5		+ 0.4	
11; M	Control	1.944			35.0			Nausea and vomiting occurred 50 min. after injection.
	1/2 hr.	2.443		+22.5	56.0		+60.0	
12; F; 42; 1.74	Control	2.454	84.3		65.2	72.9		Feeling more comfortable.
	1/2 hr.	2.533	87.0	+ 3.2	70.7	79.1	+ 8.4	
	1 hr.	2.556	87.8	+ 4.2	70.7	79.1	+ 8.4	
13; F; 42; 1.64	Control	2.268	79.3		31.5	37.4		Drowsy during first 3/4 hr. Then felt "awake" and much better. Wheezing had disappeared.
	1/2 hr.	2.394	83.7	+5.6	31.5	37.4	0	
	1 hr.	2.835	99.2	+25.0	34.1	40.5	+ 8.3	
14; M; 35; 2.35	Control	2.861	65.9		68.0	42.5		Marked improvement.
	1/2 hr.	3.047	70.2	+ 6.5	88.0	55.0	+29.4	
	1 hr.	3.255	75.0	+13.8	96.0	60.0	+41.2	

per cent (80.0 per cent of the predicted value), and the greatest decrease was 17.9 per cent (57.5 per cent of the predicted value).

2. Maximal Breathing Capacity: The maximal breathing capacity at one-half hour after the administration of Demerol was improved in seven, diminished in four and unchanged in two patients. At the end of an hour the maximal breathing capacity was improved in five, decreased in six and

unchanged from the control performances in two instances (table 1). The greatest increase of the maximal breathing capacity was plus 64.3 per cent (85.5 per cent of the predicted value), and the greatest decrease was minus 40.0 per cent (17.9 per cent of the predicted value).

3. Respiratory Rate: The respiratory rate increased slightly in several patients after Demerol. It was diminished by one or two respirations per minute in two and unchanged in one patient (table 2).

TABLE II

Changes in Pulmonary Ventilation after Single Injection of Demerol (subcutaneously) during Acute Attack of Bronchial Asthma

Patient	Time	Resp. Rate	Tidal Vol. (L.)	Total Min. Vent. (L)
1	Control	16	0.621	9.934
	1/2 hr.	24	0.451	10.828
	1 hr.	20	0.234	4.672
2	Control	21	0.760	15.952
	1/2 hr.	27	0.535	14.454
	1 hr.	24	0.558	13.390
3	Control	16	0.587	9.393
	1/2 hr.	17	0.658	11.189
	1 hr.	17	0.677	11.501
4	Control	15	0.692	10.379
	1/2 hr.	13	0.617	8.018
	1 hr.	17	0.687	11.679
5	Control	14	0.699	9.784
	1/2 hr.	13	0.671	8.717
	1 hr.	11	0.701	7.710
10	Control		1.550	
	1/2 hr.		1.000	
	1 hr.		0.890	
13	Control	13	0.627	8.150
	1/2 hr.	16	0.503	8.040
	1 hr.	15	0.473	7.090
14	Control	14	0.944	13.200
	1/2 hr.	14	0.813	11.380
	1 hr.	15	0.730	11.290

4. Tidal Volume: The tidal volume was generally diminished in seven patients at one-half hour and in five patients at one hour after the injection. In only two determinations was the tidal volume increased, and in two it was unchanged (table 2). The maximal decrease was minus 42 per cent from a control reading of 1,550 c.c. to 890 c.c. In only one patient did the tidal volume decrease to an abnormally low value, namely, 234 c.c. In all other patients the tidal volume, even though decreased after Demerol, remained well within normal range, 473 c.c. to 730 c.c.

5. Total Minute Ventilation: The total minute ventilation was generally decreased after Demerol. The decrease was recorded in 11 instances, against

TABLE III

Arterial Blood Studies after Single Injection of Demerol (subcutaneously) during Acute Attack of Bronchial Asthma

Pt.	Time	CO_2 Content (Vol. %)	O_2 Content (Vol. %)	O_2 Satur. (%)	pH	Chloride (mEq./L.)	Hgb. (gm.)	Hct. (%)
1	Control	53.59	13.81	78.98	7.38	100	13.07	38
	1 hr.	53.59	13.05	74.53	7.33	99		
2	Control	41.31	16.78	95.56	7.36	103	13.10	41
	1 hr.	41.52	16.68	94.99	7.38	101		
3	Control	41.52	11.50	80.20	7.38	106	10.70	32
	1 hr.	40.04	11.17	77.89	7.37	110		
4	Control	42.23	18.37	90.99	7.41	89	15.07	44
	1 hr.	42.04	18.25	90.39	7.32	87		

an increase in only three determinations (table 2). The control values ranged from 8.150 L. to 14.454 L., and after one hour from 4.672 to 13.390 L.

6. Arterial Blood Analyses: Arterial blood studies were carried out in four patients before and one hour after the administration of Demerol. The data are listed in table 3. The highest hematocrit was 44 per cent, with a hemoglobin of 15.0 gm. Two patients were slightly hypoxic, with oxygen saturation values of 78.98 and 80.20 per cent. Their carbon dioxide content was not elevated, the highest value being 53.59 vol. per cent. The pH values and the chloride determinations were normal. One hour after Demerol the changes from the control values were slight.

DISCUSSION

It is widely accepted that morphine and its derivatives are generally contraindicated in asthmatic patients because of marked respiratory depressing action. Since the various studies by others demonstrated that Demerol has minimal depressing effect on the respiratory mechanism of the normal subject, its effect on respiration in the patient with pulmonary disease (specifically, bronchial asthma) was investigated. The usefulness of Demerol in the asthmatic patient is stressed, whether it be used for its analgesic-sedative effect or for the relief of the acute bronchospasm by virtue of its antihistaminic and anticholinergic properties.

Our experimental studies have demonstrated that Demerol has both antihistaminic and anticholinergic properties. These pharmacologic properties would indicate its usefulness in bronchial asthma.[22] There have been a large number of clinical observations attesting to both the safety and the effectiveness of Demerol. Our pulmonary function studies clearly support these clinical observations.

Total minute ventilation dropped toward the normal range after Demerol in most of our patients. Marked hyperventilation was notably diminished,

without a rise in the arterial blood carbon dioxide content. The alveolar ventilation was not reduced by the decrease in total ventilation. It appears, however, that alveolar gas exchange did not improve materially, since the arterial blood oxygen content did not increase at one hour after the administration of Demerol. Significant respiratory depression or respiratory acidosis did not occur.

Bronchospasm diminished to various degrees in most patients in that they demonstrated less wheezing and an improved vital capacity and maximal breathing capacity; in others the excessive relaxation, drowsiness or nausea caused by Demerol actually interfered with the execution of these tests. However, even the patients whose vital capacity or maximal breathing capacity after Demerol was decreased stated that they felt more comfortable and that their breathing was easier.

These laboratory findings confirm our extensive clinical experience with Demerol in the management of the seriously ill patient with bronchial asthma.[16]

Demerol can of course depress respiration if given in too large a dose or if repeated too frequently in patients with chronic bronchial asthma and associated emphysema. It should be used with great caution when given in combination with barbiturates, especially in patients with chronic hypoxia secondary to chronic pulmonary emphysema. In the later stages of chronic pulmonary emphysema, as arterial hypoxia and hypercapnia become more pronounced, the carbon dioxide intoxication syndrome occurs more commonly. The zealous physician, affording relief from dyspnea with "adequate" sedation and "treating" hypoxia with high concentrations of oxygen, will encounter this syndrome all too frequently. We described the mechanism of death in patients with chronic cor pulmonale associated with kyphoscoliosis or chronic pulmonary emphysema who had received such therapy.[34, 35] We recently described the use of the remarkable morphine antagonist, Nalline (N-allylnormorphine), in several such instances with life-saving results. With its prompt intravenous use, the respiratory rate improved and a prompt and pronounced drop in the abnormally high pCO_2 and a progressive rise of the pH toward normal were observed.[34]

Demerol in the proper dose in accordance with the patient's age and size has proved to be an important drug in the treatment of the severe acute asthma attack, and in status asthmaticus in particular. The use of Demerol for a total of two to five days, administered at intervals of six to eight hours orally or parenterally, has not caused addiction in our patients, even when this course was repeated at several weeks' interval. We do not recommend its routine use in any of these patients.

Summary

1. Demerol, 100 mg. subcutaneously, given to asthmatic patients, demonstrated by means of protection studies very good anticholinergic action and fair antihistaminic action.

2. Pulmonary function studies performed before and after the administration of 50 to 100 mg. of Demerol subcutaneously in patients with acute bronchial asthma demonstrated diminished hyperventilation in all of the patients, an increase of the vital capacity and maximal breathing capacity in most patients, and slight respiratory depression in one patient. Arterial blood studies in four patients showed no significant changes in the blood gases or pH.

3. Mild side reactions were seen in several patients. These consisted of dizziness, sleepiness, nausea and vomiting. Severe respiratory depression and respiratory acidosis were not observed in our subjects.

4. Demerol should not be given in combination with barbiturates or along with high concentrations of oxygen in patients with chronic hypoxia secondary to chronic pulmonary emphysema. Nalline (N-allylnormorphine) intravenously should be administered promptly if respiratory depression is noted in these patients.

5. Demerol, used in proper dosage, is a very useful and safe drug in the treatment of the patient in an acute asthma attack or in status asthmaticus when the usual methods of treatment have failed or fastness to epinephrine or aminophylline has developed.

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STUDIES ON "ESSENTIAL" HYPERTENSION. V. AN ENDOCRINE HYPERTENSIVE SYNDROME *

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THERE is no evidence that so-called "essential" hypertension is a single disease. In fact, the varied clinical picture strongly suggests that it is merely a syndrome caused by several pathogenetic mechanisms, in which a common predisposition and a common pathologic sequence of events have obscured essential differences between types. This belief has afforded the opportunity for a critical analysis of patients in order to observe and evaluate significant differences, and to attempt to discover objective diagnostic procedures.

Four types of arterial hypertension have been delineated and described.[1] There is the variety in which renal factors, especially organic renal parenchymal disease, appear to initiate or modify unfavorably the course of hypertension.[2, 3] There is the variety, so far poorly studied, in which late onset (fifth and sixth decades) and the presence of general arteriosclerosis appear to be the predominant features. There is the "neurogenic" type, characterized by disorders of personality, fluctuating blood pressure and onset relatively early in life,[4] which appears to be quite "benign" for many years; a response of the vessels of the skin to histamine by producing a "diencephalic" blush is diagnostic.[5] There is a fourth variety which is believed to be accompanied by a disturbance of the endocrine system, whether in an initiating or a secondary rôle, and which is reported herewith. While differentiation of the other types is often difficult when an adequate history is unavailable, the one discussed here is relatively easy to identify.

Lack of understanding of pathogenesis has prevented the adoption of an etiologic term for the syndrome seen in women with hypertension, central obesity, menstrual irregularities and low sodium chloride concentration in sweat. As a descriptive nickname the term pseudo-Cushing's syndrome has been employed,[6] but the use of the names of physicians is confusing and unjustifiable in modern medicine, and Cushing's syndrome is not enough of an entity for descriptive purposes. Therefore the broad designation "endocrine hypertensive syndrome" has been chosen in the hope that the term itself will stimulate investigation toward etiologic designation.

Several forms of "essential" hypertension associated with endocrine

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disturbances have been recognized. One is that described by Boas and Shapiro,[7] consisting of a high basal metabolic rate without signs of hyperthyroidism; it was called "non-goitrous thyrotoxic hypertension." Further diagnostic breakdown has made this type of case rare. "Menopausal hypertension" [8] has been considered a separate entity, but definitive characteristics other than the association of an elevation in blood pressure with the climacteric are lacking in these two conditions, which coexist frequently in the fifth and sixth decades. A syndrome of hypertension, obesity and diabetes was described by Herrick [9]; both diabetes and obesity have often been implicated as a contributing factor to hypertension. There are other endocrine disturbances associated with hypertension, but causal relationship has not been established for most of them. The present report discusses a clinical syndrome which can be differentiated by history, physical findings and laboratory examination [10, 11, 12] from the usual case of "essential" hypertension.

Material and Methods

Patients were studied in the Hypertension Clinic of Washington University and in Barnes Hospital. The clinic population comprises approximately 300 unselected * hypertensive patients of all types and descriptions, with a ratio of women to men of 3 : 1. Careful histories and routine laboratory examinations with attention to renal function were obtained in every case; special studies, such as the reaction of the blood pressure to tetraethylammonium chloride and the concentration of sodium and chloride in sweat, were performed in most. When hospitalized, patients were subjected to thorough examination of heart and kidneys. A special questionnaire for history, physical examinations and laboratory findings was completed in each. Attention was given to (1) changes in body weight: a gain of 40 pounds within a year was considered significant; (2) menstrual history: irregularities, early or late menarche, changes after pregnancy and operation on the genital organs were noted; (3) the date of onset of hypertension was discovered, if possible; (4) the presence or absence of central obesity was determined; (5) acne, hirsutism, "buffalo hump," striae on buttocks, thighs and upper arms and spontaneous ecchymoses were described; (6) glycosuria, tolerance to ingested or injected glucose, eosinophilia and lymphocytosis were recorded; (7) special studies relative to the anterior pituitary and adrenal cortex were made in some cases.

Results

Women belonging to the category of the endocrine hypertensive syndrome were estimated as comprising approximately 20 per cent of the female

* Patients over 60 and those with congestive circulatory failure or cardiac valvular disease were fairly well excluded from the clinic.

hypertensive population.† Forty consecutive cases were chosen; many others could have been included, since the condition is common and can be suspected upon inspection from a distance with a fair degree of accuracy. An attempt was made not to exclude cases from this series because of minor variations from the prototype. In table 1 associated disturbances were compared with those in Cushing's, the adrenogenital syndromes and other conditions. While all of the cardinal signs and symptoms of Cushing's syndrome were not present in any patient, each exhibited one or more of

TABLE I

Frequency of Occurrence of Signs and Symptoms in the Differentiation of Endocrine Hypertensive Syndrome from Other Endocrine Disturbances and the Effect of ACTH

Sign	Endocrine Hypertensive Syndrome	Cushing's Syndrome		Adrenogenital Syndrome	Ovarian Hyperfunction	Menopause	ACTH Administration
	per cent	per cent (1)	(2)	0-+++	0-+++		
Central obesity	100	97	97	++	+++	+	Fairly common
Moon-face	79	Very common		++	+++	+	Fairly common
Pale striae	78	Uncommon		++	++	0	Fairly common
Buffalo hump	43	Common					Fairly common
Rapid gain in weight	56	Common		?	?	++	Fairly common
Menstrual disturbance (3)	74	71	86	+-++	++++	++++	Fairly common
Gynecologic operation	47						
Hypertension	100	85	84	++		+	60% (5)
Low salt conc. in sweat (4)	85	100		++	?	?	100% (6)
Hyperchloremia	60	0			?	?	
Tendency to edema	42	Common					42% (7)
Easy bruising	60	23	60		+++	+	Occurs
Acne	21	26	82	+++	+++	?	25%
Purple striae	0	60	71	+	?	0	
Hirsutism	40			++++	+++	+	24%
Enlarged clitoris	5			++++	++	0	
Deep voice	0			++++	++	+	
Atrophy of breasts	0			++++	0	++++	0
Osteoporosis	0	95		+	?	+	Fairly common
Disturbed carbohydrate metabolism	25	49		+	?	?	11%
Muscular weakness	Uncommon	83	50	0		0	
Muscular strength				++++	+++	0	
Polycythemia	7	10		0	0	0	

(1) Previously reported.[35]
(2) Columbia series.[36]
(3) Including amenorrhea.
(4) Below mean value for normotensive women in summer. Some of the tests were done in winter, when the salt concentration in sweat is elevated.
(5) Greater than 10 mm. Hg rise in diastolic B. P.
(6) Reference.[36]
(7) Occult edema.

them (table 2). If all of the findings in these women were consolidated into one case, that case would have Cushing's syndrome without osteoporosis.

Hypertension was often severe but rarely malignant. It was frequently accompanied by hemorrhagic and exudative lesions in the ocular fundi and

†Of 100 unselected patients studied at the Hospital of the Rockefeller Institute in 1937–42, comprising 43 males and 57 females, 12 cases of this variety were found.[1] The incidence of 12 per cent of all cases and 21 per cent of all female hypertensive patients is similar to that in the present larger group.

Fifty cases of the endocrine hypertensive syndrome were seen in approximately 200 female out-patients; 18 were found in 95 private patients.

TABLE II
Findings in 40 Cases of the Endocrine Hypertensive Syndrome

1	2	3	4	5	6	7	8	9		10	11	12	13	14	15	16	17	18
Patient No.	Age	Age at Onset of Hypertension	Rate of Weight Gain	Maximal Weight	Age at Most Rapid Gain	Initiating Factor of Obesity	Menstrual Abnormalities	Pregnancies: Gravida	Pregnancies: Para	Gyn. Disturbances or Operations	Striae	Buffalo Hump	Hirsutism	Acne	Carbohydrate Disturbance	Easy Bruising	Albuminuria	Average Height of Blood Pressure
	Yrs.	Yrs.	Lbs./Yr.	Lbs.	Yrs.													Mm. Hg
L. Ni 1	47	<46	70	246	24	Miscarriage	+	3	2	0	++++	+	+	0	0	+	0	180/110
M. Pa 2	34	23	45	234	12	Menarche	+	5	5	0	++++	+	0	0	0	0	+–0	200/130
L. Re 3	27	27	20	160	23		0	*0*	0	3	++	0	0	+	0	+	++–0	130/100
R. Sp 4	52	48	3	230	27	Pregnancy	+	4	4	0	+	0	+	+	0	+	±	130/80
L. Ro 5	34	26	50	291	22	Marriage	+	*0*	0	1	++++	+	+	+	0	+	0	210/130
M. Le 6	37	36	40	224	33	Amenorrhea	+	1	1	2, 4	++++	+	+	+	0	+	0	180/110
M. La 7	47	43	50	230	29	Puerperal sepsis	+	11	11	0	++++	+	0	0	0	+	0	240/130
R. Sh 8	48	<42	65	238	20	Pregnancy	+	3	3	1, 4	++++	+	0	0	0	++++	0	150/100
S. Mo 9	58	50	16	195	49	Menopause	+	2	2	0	0	+	0	0	+	±	+	150/95
F. Ra 10	40	39	30	194	29	Pregnancy	0	6	5	2	++++	+	±	0	0	+	+	160/100
J. Ke 11	40	<40	30	161	25	Pregnancy	0	2	2	0	++++	0	0	0	0	++	0	155/105
E. Ru 12	41	<39	30	205	21	Hysterectomy	0	1	1	1	++++	+	0	+	0	++++	+	200/140
L. Pr 13	42	<42	25	336	36	Hysterectomy	+	2	2	1, 3	++	+	0	0	0	0	+++	260/160
G. Hu 14	37	<35	3.0	230	11	Menarche	0	1	*0*	1, 3	+	0	+	0	0	0	0	150/100
M. Hi 15	44	34	75	290	35	Pregnancies	0	8	8	0	++++	+	0	0	0	++++	0	200/125
E. Cl 16	53	40	5.8	181		Marriage	0	11	8	1, 3	+	0	0	0	0	+	0	190/105
O. W. 17	35	34	1.8	184	31	Marriage	+	5	5	0	+	0	0	0	0	0	0	145/115
E. Bl 18	53	41	30	230	39	Radiation to pelvis	+	2	2	5	+	0	0	0	+	+	+++	300/150
S. Pe 19	44	27	48	223	27	Pregnancy ?	0	1	1	1, 3	0	0	0	0	0	0	±	162/114
B. El 20	48	35	40	208	45	Amenorrhea	+	5	*0*	0	0	0	0	0	0	+	±	180/158
F. Ro 21	54	39	5	182	25		+	*0*	0	+	+	0	0	0	0	+	0	160/140
B. Da 22	47	<40	26	186	27	Appetite	+	*0*	0	1, 3	+	0	0	0	0	0	0	220/130
I. Ha 23	40	28	25	215	38	Operation	+	2	*0*	1	0	0	0	+	0	+	+	190/126
M. Ne 24	31	<31	6	200	20		+	1	1	0	+	0	0	0	0	+	0	180/120
A. Fi 25	49	35	4.4	153	35	Operation	+	1	*0*	1, 3	0	+	0	0	0	0	+	210/120
H. Pu 26	37	34	29	270	11	Menarche	+	1	*0*	0	0	+	0	+	0	++	++++	262/156
E. Bl 27	36	29	5	181	27	Marriage	+	2	*1*	1	+	0	+	+	0	+	0	175/102
M. Kr 28	34	20	61	263	20	Pregnancy	+	3	*1*	2	+	0	+	+	0	0	0	220/130
M. Ph 29	50	41	13	230	20	Marriage	?	2	2	1	+	0	+	+	0	0	0	200/110
I. Fr 30	52	48	3	168	39	Operation	+	2	2	1, 2	++	0	+	+	0		±	205/120
H. Bl 31	29	20	150	285	29		+	5	4	0	+	0	0	0	+	0	0	190/130
M. Ph 32	47	42	42	185	46		+	*0*	0	1, 3	0	0	0	+	0	0	+	187/122
A. Wi 33	39	38	gradual	197	gradual		+	3	*0*	0	+	0	+		0	0	0	160/100
H. Sp 34	57	51	16	235	21		+	*0*	0	1, 3	0	0	+	0	0	+	0	160/95
M. St 35	34	24	30	160	33	Pregnancy	+	2	2	2		0	0	0	0	+	0	180/110
L. Sm 36	49	41	6	216	38	Pregnancy	+	2	2	1, 3	+	+	+		+	+	0	200/120
L. Sp 37	47	46	26	276	46		0	5	*3*	0	+	0	0	0	0	0	0	175/110
O. He 38	50	49	3	162	48	Appetite	+	4	4	0	+	0	+	0	0	+	+	190/104
M. Lo 39	44	43	54	200	44		+	3	3	5	0	0	0	0	0	+	+	180/160
M. Sc 40	49	47	8	211	30		+	*0*	0	0	+	0	+	0	0	+	0	141/92
n =	40	40	38	40	37		38	40	40	40	39	40	40	38	40	40	40	40
Mean or cases positive	42.9	36.9	29.7	217	30		29	2.83	2.18	24	30	18	16	8	10	24	18	186/117
Per cent							76%			60%	76.9%	45%	40%	21%	25%	60%	45%	

(1) Hysterectomy. (2) Oophorectomy. (3) Myoma present. (4) Ovarian tumor or cyst present. (5) Radium implantation.

papilledema which regressed and reappeared. Other pathologic changes secondary to hypertension occurred in the usual frequency. One important difference was noticed: in spite of the presence of severe hypertension there was often little or no albuminuria, little or no evidence of depression of renal function by the usual clinical tests, and few signs of progressive renal damage.

Clinical Description

The typical sequence of events encountered in one-half of these patients was a sudden gain in weight following some physiologic, pathologic or iatrogenic disturbance of the genital system (menarche, pregnancy, growth of tumor, operation) occurring some time before the onset of hypertension. Often patients were thin until this event. Reduction in weight became very difficult and slow, even on severe caloric restriction. The weight was distributed about the buttocks, thighs, thorax and upper arms; the extremities were wedge-shaped. Forearms were often muscular but not obese, and the hands and wrists were small and free of excess fat, as were the feet and ankles. A large panniculus was present. A "buffalo hump" with moderate kyphosis, and sometimes a fat pad over the lower cervical vertebrae (in 45 per cent), resembled that seen in Cushing's syndrome.

Central obesity was present in all cases except for one who had voluntarily reduced to a normal weight but who had given the history of gaining from 100 pounds to 184 pounds at the age of 31. The rapidity of the gain in weight was often striking, subsequent disturbances such as pregnancy apparently initiating further gain. Rapid gain in weight was not present in half of the patients who claimed that they had "always" been obese; close questioning usually revealed that obesity began suddenly with the menarche and progressed slowly thereafter.

Weight: The average age at which weight was gained rapidly was 30 years, varying from a low of 12 years to a high of 50 years. In three cases the weight gain was gradual, having begun at the menarche and continuing thereafter at a steady rate. The average maximal weight of all patients was 215 pounds, ranging from 160 pounds to 336 pounds. The average gain per year was 30 pounds at the time of the rapid gain, ranging from a few pounds to a high of 75 pounds. In one case 75 pounds was gained within six months. In all cases the obesity was most marked in the trunk; in many the proximal parts of the extremities and the face were also involved. Twenty-one of the patients had faces which definitely could be described as moon-shaped, and the remainder exhibited this tendency. The average height of these patients was on the short side, many of them being not much more than five feet two or three inches tall.

Coincidental with the gain in weight was the menarche in three cases, marriage in five, pregnancy in 10, operations on the pelvic organs in six, sudden increase in appetite in two, amenorrhea in two and emotional dis-

turbances in two. In the remainder no associated disturbance could be discovered.

Hypertension: In no case was the presence of hypertension established before the gain in weight. The average age at onset of hypertension was 36.9 years, some seven years after the average age at which weight was gained. In nine cases hypertension began before the age of 30, but in only one was it discovered after the age of 50. The average age at the time the patients were first examined was 42.9 years. The mean blood pressure of the whole group when observed was 186 mm. Hg systolic and 117 diastolic.

Menses: The menarche occurred from the ages of 11 to 14, with two exceptions, in whom it occurred at 16. There appeared to be no complicating disturbances associated with its appearance. The menopause or cessation of menses had occurred in 19 of the 40 patients, but in no case was the rapid gain in weight associated with spontaneous menopause occurring at the usual age.

TABLE III

Number of Gynecologic Operations in Normotensive and Hypertensive Obese Women Paired as to Age

	No. of Patients	Mean Age	Mean Max. Weight	Mean B. P.	No. of Patients with History of Gyn. Operation
Obese Hypertensive Women	15	51.4	212	205/116	10
Obese Normotensive Women	15	51.2	211	135/84*	3

* Nine patients.

Note: These patients were paired as to age and weight; they were selected from 690 obese patients attending the Washington University Food Clinic for diets containing 1,400 calories or less. The small numbers available indicate the very few normotensive obese women over 50 years of age; only 15 were found. The hypertensive obese women were not chosen from the group here reported.

Twenty patients had been subjected to operations on the uterus or ovary. Eleven had had fibroid tumors removed, two ovarian tumors or cysts, and the remainder various pelvic operations with removal of an ovary and tube; one had had radium implantation after a dilatation and curettage. Table 3 shows that a history of gynecologic operations is more frequently encountered in obese women with hypertension than in those of similar age and weight without hypertension. Five had developed toxemia of pregnancy and seven had had miscarriages. The average number of pregnancies was 2.83, and the average number of children born alive was 2.18. No pregnancies had occurred in seven, although all were married. Thirteen patients had had miscarriages. On the other hand, six had had five or more successful pregnancies, and one had had 11. In no case was there completely normal function of the reproductive system. Of the eight women without menstrual irregularities or abnormalities, hysterectomy had been performed in five, two had had repeated miscarriages, and one had suffered a toxemia of pregnancy. With a possible exception of the last, in every

case there was some disorder, either functional or organic, of the female generative tract.

Irregularity of the menses was the rule (74 per cent); often menses became irregular with the onset of the obesity. Premenstrual headaches were usual. The menses varied from profuse to scanty; irregularity, rather than any set pattern, was the principal characteristic. Toxemia of pregnancy was seen not infrequently at the onset or after hypertension had become established.

Other Signs and Symptoms: Hirsutism was encountered much more commonly (40 per cent) than in a similar group of normal women. It ranged from the extremes of a heavy growth of beard in two cases to a light but definite mustache. Hair on the chin and upper lip was found in 12 of the 16 with hirsutism. The others exhibited a masculine distribution of hair and excessive hair on the extremities. Only four showed a tendency to baldness. Absent or scanty peripheral body hair was encountered, and axillary hair was thin in some.

Many patients demonstrated abnormal dietary habits as to the ingestion of water and salt. Eighteen stated that they had a preference or craving for salt and appeared to like plenty in their food. Only four said that they did not like salt. One-half of the patients said that they liked to drink much water. Sixteen (or 40 per cent) showed a tendency to edema of the ankles, although there were no signs of cardiac decompensation. It was difficult to differentiate natural tendencies from those superimposed by teaching and habit, but in many cases the trends were striking.

History of spontaneous ecchymosis and easy bruising were found in 60 per cent. Acne was not unusual (21 per cent). Enlargement of the clitoris was found in only two, demonstrating minor degrees of the adrenogenital syndrome. Slight polycythemia up to 6 million red blood cells per cubic millimeter was present in only three. There was no tendency for lymphopenia as seen in the routine blood count, nor was there eosinopenia. In six of the 10 patients in whom it was measured there was a tendency for the chloride level of the plasma to be slightly elevated, up to 113 mEq. per liter, with depression of carbon dioxide combining power. Sodium and potassium levels of the plasma were normal. Abnormal carbohydrate metabolism was quite often encountered (25 per cent), ranging from frank "diabetes" to abnormally low tolerance to ingested or injected glucose. Increased insulin sensitivity was found in a few cases; no patient was resistant to its action. A history of "diabetes" clearing spontaneously suggested an unusual form of carbohydrate disturbance. The sodium chloride content of sweat was reduced in most cases to levels much below normal, as reported by Davies and Clark.[11] The normal value in winter of the sodium concentration in sweat is 57 mEq. per liter. Twenty-one of 26 had a sodium concentration in sweat, 30 minutes after exposure to a steam room during the winter, below 28.1, i.e., the mean value for obese normotensive women in summer. The summer value is roughly half the winter value. An objec-

tive diagnostic test was thereby offered for this syndrome, dependent only on the exclusion of other conditions causing low concentration of salt in sweat; there are very few.

Pathologic Findings

Of those women diagnosed as having the endocrine hypertensive syndrome during life, only five have come to autopsy. All showed left ventricular hypertrophy, slight to moderate arteriolar nephrosclerosis, polyps or myomata of the uterus, and adenomata or focal hyperplasia of the cortex of the adrenal gland. In two others subjected to operation, adenomata of the adrenal cortex were found and removed (cases 5 and 6). Therefore, pathologic records containing the accessory diagnosis of adenoma or focal or diffuse hyperplasia of the adrenal cortex were examined.

In 4,000 consecutive autopsies on adults made between 1944 and 1950, 71 cases with one of these diagnoses were found, an incidence of 1.75 per cent. There were 32 women and 39 men. Statistical comparison of incidences was not made at this time, for the purpose of the study was to examine the associated disturbances; the diagnosis of adrenal cortical hyperplasia or adenoma when made was accurate, but its presence or absence depended somewhat upon the enthusiasm and care of the prosector in obtaining sections of the adrenal glands, and therefore cases may have been undiscovered.

Tables 4 and 5 list the associated disturbances. In 85 per cent (60 cases) the male heart weighed 350 gm. or more, the female heart 300 gm. or more, and in 70 per cent more than 400 and 350 gm., respectively. Judging by the formula of Smith,[18] based on body weight, all hearts but four were enlarged 75 gm. or more over their predicted sizes. None showed evidence of valvular disease.

Arteriolar nephrosclerosis was absent in 15 cases with cardiac hypertrophy, was of slight degree in 26, of moderate degree in 21, and advanced in six. Thirty-three cases were proved to have exhibited chronic arterial hypertension; nephrosclerosis was absent in five and slight in 10.

Protocols and histories were deficient in most cases to indicate the presence of preëxisting central obesity. There were, however, 16 cases (of 32) who were obese hypertensive women with gynecologic disturbances; three were diabetic. We believe that they represented the endocrine hypertensive syndrome. In five others the data were suggestive but incomplete. Of interest is the extraordinarily high incidence of uterine myomata (56 per cent); in 29 some alteration of the female reproductive organs was found (90 per cent). The presence of hyperostosis frontalis interna was frequently noted when x-ray photographs of the skull had been made, in both the pathologic and the clinical material. There was no special attempt to obtain routine x-rays of the skull. In a previous unpublished study one of us (H. A. S.) found that nine of 12 cases of the endocrine hypertensive syn-

TABLE IVa

Adenomata and Focal Hyperplasia of Adrenal Cortex
4000 Autopsies (Males)

Case No.	Age, Race	Criteria of Hypertension			B. P. mm. Hg	Body† Weight kg.	Obesity Noted	Adrenal Glands		Other Findings	Cause of Death
		History	Cardiac Weight gm.*	Arteriolar Nephrosclerosis				No. Adenomata	Wt. gm.		
1	43 W	+	*890*	Adv.	234/134	87	+	1	25.8		Cerebral hemorrhage
2	58 W	+	*710*	Adv.	230/130	77	0	1	22		Cerebral hemorrhage
3	71 W	+	*710*	Mod.	50/?	96	+	2	19.5		Dissecting aneurysm of aorta
4	48 W	+	*630*	Mod.	120/82	80+20	+	1	26	Central obesity and striae	Coronary occlusion
5	59 W	+	*610*	Mod.	230/130	85	+	Several	22.5	Diabetes, cirrhosis of liver	Intercapillary glomerulosclerosis
6	70 W	−	*570*	Mod.	90/70	91	+	1	28		Ependymoma
7	46 W	+	*530*	—	—	60	−	3	17		Cardiac failure
8	74 W	−	*530*	Sl.	100/70	55+10	0	1	14	Easy bruising	Carcinoma of bladder and prostate
9	45 W	0	*525*	0	144/80	61	0	1	21	Asthma	Bronchiectasis
10	45 W	+	*510*	Sl.	136/100	88	+	1+	28	Cortical cell carcinoma	Coronary occlusion
11	81 W	−	*500*	Mod.	130/80	—	−	1	31.5	Carcinoma of prostate	Post-op. peritonitis
12	65 W	−	*470*	Mod.	120/70	64	0	Accessory tissue	21		Coronary thrombosis
13	60 W	−	*460*	0	176/90	80	0	1	47		Monocytic leukemia
14	76 W	−	*450*	Sl.	125/80	80	+	1	22	Hyperplasia of prostate; pancreatitis	Pulmonary thrombosis
15	75 W	−	*440*	Mod.	160/75	—	−	Several	20		Coronary thrombosis
16	62 W	−	*440*	Sl.	—	*80*	+	1	30		Coronary occlusion
17	56 W	−	*430*	Sl.	125/80	54.5	0	1	25		Carcinoma of bronchus

TABLE IVa—*Continued*

Case No.	Age, Race	Criteria of Hypertension			B. P. mm. Hg	Body† Weight kg.	Obesity Noted	Adrenal Glands		Other Findings	Cause of Death
		History	Cardiac Weight gm.*	Arteriolar Nephro-sclerosis				No. Adenomata	Wt. gm.		
18	64 C	−	*430*	Sl.	—	78.5	+	Many	17	Aneurysm of aorta	Carcinoma of tongue
19	62 W	−	*420*	Mod.	180/80	—	0	1	30	Diabetes	Pyemia
20	67 W	−	*410*	Sl.	—	70+30	Prior	1	27		Post-op. anuria
21	68 W	−	*400*	Sl.	140/70	83	+	22	22	Intercapillary glomerulosclerosis	Pseudomyxoma of peritoneum
22	56 W	−	*400*	0	130/100	93	+	Many	59	Adenomas of pancreas; pituitary eosinophilia	Peptic ulcer
23	50 W	+	*400*	0	176/90	80	0	1	18		Carcinoma of larynx
24	47 W	−	*400*	Sl.	—	81	0	Several	23	Easy bruising	Fibroblastoma of arachnoid
25	71 W	−	*380*	—	126/90	—	0	1	18		Exfoliative dermatitis
26	65 W	−	*380*	Mod.	—	—	0	2	30		Coronary occlusion
27	48 W	−	*350*	Mod.	—	70	—	Several	44	Easy bruising	Sarcoma of meninges
28	69 W	−	*350*	0	130/85	75	0	Several	23	Hyperplasia of prostate	Nephrolithiasis
29	68 W	−	*335*	Mod.	104/80	60	—	1	24		Carcinoma of bronchus
30	41 W	+	*330*	0	160/90	65+20	Prior	Several	31		Carcinoma of islets of Langerhans
31	46 W	−	*280*	0	—	41	—	1	31	Cachexia	Carcinoma of prostate
32	41 W	−	*250*	0	92/52	41	—	1	21	Cachexia	Carcinoma of colon

* Nonvalvular heart disease.
Weight in italics signifies that the heart is enlarged 75 gm. or more than normal according to the formulae:
Male heart weight (gm.) = 0.43 × body weight (kg.)
Female heart weight = 0.4 × body weight (kg.).
Case number in italics signifies that the endocrine hypertensive syndrome was probably present.
† Body weight at autopsy. Plus values indicate maximum weight by history.

TABLE IVb

Adenomata and Focal Hyperplasia of Adrenal Cortex
4,000 Autopsies (Females)

Case No.	Age, Race	Criteria of Hypertension			B. P. mm. Hg	Body Weight kg.	Obesity Noted	Adrenal Glands		Other Findings	Cause of Death
		History	Cardiac Weight gm.*	Arteriolar Nephrosclerosis				No. Adenomata	Wt. gm.		
1	44 W	+	*640*	Mod.	300/140	74	+	1	35	Myomata of uterus	Cerebral hemorrhage
2	53 C	+	*550*	Sl.	240/160	Marked central obesity		1	20	Hirsutism	Pulmonary edema
3	76 W	+	*540*	Mod.	220/130	60	+	1	17	Osteoporosis	Cerebral thrombosis
4	76 W	−	*500*	Sl.	100/60	75	+	1	27	Cervical polyps	Mesenteric thrombosis
5	81 W	−	*470*	Mod.	160/60	55	0	1	25	Osteoporosis	Mesenteric thrombosis
6	77 W	+	*450*	Sl.	200/120	53	+	1	26	Myomata of uterus	Pulmonary thrombosis
7	47 C	+	*440*	Adv.	220/140	—	—	1	30	Myomata of uterus	Cerebral hemorrhage
8	55 W	−	*430*	0	—	69	0	1	17	Cyst of ovary	Carcinoma of bronchus
9	58 W	+	*420*	Sl.	220/130	*95*	+	Ca	24.4	Myomata of uterus	Carcinoma of adrenal cortex
10	67 W	+	*410*	—	200/75	55	0	Several	30		Multiple vascular thrombi
11	56 W	+	*385*	Sl.	160/100	*75*	+	1	21	Myoma of uterus	Meningioma
12	68 W	+	*380*	Sl.	188/110	58.5	+	Many	14	Myomata of uterus	Melanoma of meninges
13	48 W	+	*380*	Sl.	120/66	57	0	Several	40	Para-ovarian cyst uremia	Scleroderma
14	68 W	+	*360*	Mod.	180/90	57	0	3	32	Myomata of uterus and stomach	Chondrosarcoma
15	42 W	+	*350*	0	185/120	55	0	1	19	Para-ovarian cyst	Chronic glomerulonephritis
16	63 C	−	*340*	Sl.	—	65	—	1	20		Carcinoma of uterus
17	50 W	+	*330*	Sl.	180/95	70	+	Several	19		Subarachnoid hemorrhage
18	52 W	+	330	0	125/70	74	+	Many	Metastases	Hirsutism, kyphosis, tumor in adrenal	Carcinoma of breast
19	48 W	−	*320*	Sl.	—	44	0	1	30		Carcinoma of cervix
20	60 W	−	270	Sl.	—	64		1	15	Panhysterectomy	Carcinoma of breast; carcinoma of ovary
21	58 W	+	*264*	Mod.	200/104	40	0	2	50	Myoma of uterus	Cerebral hemorrhage
22	42 W	−	250	0	—	55.8	0	1	12.5	Myomata of uterus	Post-op. for pneumonectomy
23	46 W	−	190	Sl.	90/60	41	0	1	20	Myoma of uterus	Carcinoma of stomach

* Nonvalvular heart disease.

Weight in italics signifies that the heart is enlarged 75 gm. or more than normal according to the formulae:

Male heart weight (gm.) = 0.43 × body weight

Female heart weight = 0.4 × body weight (kg.).

Case number in italics signifies that the endocrine hypertensive syndrome was probably present.

TABLE Va

Hyperplasia of Adrenal Cortex

(Males)

Case No.	Age, Race	Criteria of Hypertension			B. P. mm. Hg	Body Weight kg.	Obesity Noted	Adrenal Glands Wt. gm.	Other Findings	Cause of Death
		History	Cardiac Weight gm.	Arteriolar Nephrosclerosis						
1	31 W	+	700	Adv.	250/140	73	+	20	Hyperplasia of islets of Langerhans	Uremia, pyelonephritis
2	71 W	+	505	Mod.	210/110	89	+	23	Diabetes, carcinoma of prostate	Cerebral thrombosis
3	54 W	−	470	Sl.			+	40		Accident
4	66 W	0	460	0	150/80	70.5		33		Post-op. cholecystectomy
5	51 W	−	350	0	115/80	Cachectic		28		Amebiasis
6	52 W	−	340	Sl.	115/70	60	0	35		Lymphatic leukemia
7	65 W	−	310	Sl.		55		31		Carcinoma of stomach

drome exhibited this abnormality; it was not present in 91 other hypertensive patients examined routinely.

Perhaps of significance is the high incidence of malignant changes in organs. There were 31 carcinomata or sarcomata in 29 cases, of which those of the ovary, uterus, breast, adrenal cortex, islands of Langerhans and prostate comprised almost half.

We have often wondered whether the syndrome occurs in males; if so, what are the criteria for its recognition? The number of males exhibiting adrenal cortical hyperplasia and adenomata was greater than that of females.

TABLE Vb

Hyperplasia of Adrenal Cortex

(Females)

Case No.	Age, Race	Criteria of Hypertension			B. P. mm. Hg	Body Weight kg.	Obesity Noted	Adrenal Glands Wt. gm.	Other Findings	Cause of Death
		History	Cardiac Weight gm.	Arteriolar Nephrosclerosis						
1	70 W	+	520	Mod.	155/90	96	+	22	Diabetes	Bacterial endocarditis
2	55 W	+	510	Mod.	175/95	70	+	25	Myomata of uterus, diabetes	Intercapillary glomerulosclerosis
3	60 W	+	440	Adv.	240/150	75	+	23	Myoma of uterus	Encephalopathy
4	59 W	+	420	0	176/80	66	+	20	Central obesity, diabetes, adenoma of ovary	Intercapillary glomerulosclerosis
5	65 W	+	400	Adv.	200/110	63	+	16	Myomata of uterus, cyst of ovary	Carcinoma of breast
6	44 C	−	380	Sl.	130/90	85	+	21	Myomata of uterus, cyst of ovary	Carcinoma of ovary
7	56 W	+	350	Sl.	190/110	48		14.5	Myomata of uterus, masculine habitus	Subdural hematoma, accident
8	44 W	−	340	0	110/78	43		15	Myoma of uterus, cyst of ovary	Disseminated lupus

All had enlarged hearts, 11 were proved hypertensives, and 16 were said to have been obese. Sodium levels in sweat were not estimated. No associated phenomena were observed with any consistency. It is probable that the syndrome does occur in men, but definite diagnostic tests have not been developed.

Discussion

The syndrome here described probably should no longer be considered as "essential" hypertension; heretofore about 20 per cent of female hypertensive patients encountered have exhibited it. The characteristic quadrad of central obesity, often with rapid gain in weight, menstrual irregularities or gynecologic disease, hypertension and low concentration of sodium chloride in sweat, is not found in the ordinary patient with "essential" hypertension. It is justifiable, therefore, to distinguish these cases on clinical and laboratory grounds in order to search for etiologic and pathogenetic factors. Attention is focused on the ovary, the adrenal cortex and the anterior pituitary. The well known ability of certain ovarian tumors to cause some of the signs suggests ovarian pathologic changes; the onset of the menopause, however, apparently did not initiate them. Hypersecretion of some portions of the adrenal cortex may also produce them, either directly or through stimulation by the anterior pituitary. We have been unable to implicate any particular endocrine organ as primarily involved, but believe that the adrenal cortex usually is hyperactive.

There are four commonly recognized causes of obesity which should be examined in relation to the "endocrine hypertensive syndrome." Psychogenic overeating is a disorder in which food substitutes for other sources of emotional satisfaction. This type of obesity cannot be excluded in patients subject to a psychosomatic disease such as hypertension. Habitual overeating, with obesity caused by a change to sedentary habits, is probably of little concern, for most of these women were normally active. Hyperinsulinism was not found—in fact, many exhibited abnormal tolerance to sugar of a diabetic type. Hypothalamic obesity secondary to lesions or to functional changes in the midbrain may explain part of this syndrome, especially in view of the possible involvement of the hypothalamus in hypertension. The distribution of fat and the association of other endocrine disturbances suggest that the glands of internal secretion are also deranged in some unknown manner. Inability to discover consistent abnormalities by laboratory methods other than those of electrolyte content of sweat does not exclude the possibility of endocrine dysfunction. Indeed, patients of the type discussed here may represent instances of mild or borderline dysfunction which cannot be measured by the gross and uncertain methods available.*

* When the salt retaining hormone of the adrenal cortex can be easily measured in urine or blood, definitive diagnosis of cases of this disturbance may be more readily made than at present.

Several similar syndromes have been reported. Sheldon [14] has described the "maternal obesity" syndrome, which represents the rapid gain in weight observed in women during pregnancy or after childbirth. Two of the 26 women reported by Sheldon gained over 120 per cent of their previous weight, one exhibited features suggestive of Cushing's syndrome, two were diabetic, six had glucose tolerance curves of a diabetic type, and several seemed to belong to the "large-baby diabetic syndrome." [15] Although the etiology may lie in the hypothalamus, two factors suggest a possible endocrine disturbance. One is the close association of obesity with the hormonal disturbances accompanying pregnancy. The other is the distribution of the obesity which was described as accumulating "especially in the proximal half of the arms, the breasts, abdomen, buttocks, and thighs. . . ." This distribution is similar to the central obesity recognized to be associated with endocrine disorders. No difference from the expected incidence of hypertension was noticed in his group.[16]

A syndrome observed among children at or before puberty has been described by Simpson as "adipose gynism," [17] characterized by excessive height, marked adiposity of central distribution, short thick neck, red lineae distensae and varying shades of plethora. Among boys it was called "gynandrism" because of the prominent female characteristics. The females "remain big and strong and adipose, are fertile and are liable to develop diabetes and hypertension." Simpson postulates pituitary-adrenal hyperfunction. Like Sheldon, he emphasizes "an imperceptible transition through the milder forms of the syndrome to accepted normality."

Alvarez and Zimmerman [18] made a thorough study of 1,230 records of blood pressure among women and concluded that ". . . a masculine distribution of body hair, sexual anesthesia, fibroids of the uterus,—and pelvic conditions requiring ovariectomy or hysterectomy are associated with high average pressures." They were led to the conclusion that hypertension is ordinarily repressed in women before the menopause by the ovarian or other related secretions. Schaeffer [8] has reported 13 hypertensive women who had what he described as a true menopausal symptom complex, who responded with a blood pressure fall during Theelin administration. This association between blood pressure and activity of the female sex organs has not been generally accepted, although no comprehensive study has been found to refute it.

Many have pointed out the wide deviations in the clinical picture known as Cushing's syndrome.[19, 20, 21, 22] The hypertension associated with it has generally been called secondary, though the proof that it is a direct effect of the endocrine disturbance is lacking. However, it is now obvious that the original description does not define the natural boundaries of a specific pathologic or clinical entity. Cases with the absence of one or more features of the original description are so numerous that Soffer,[21] Selye,[22] Hartman and Brownell [20] and Williams [19] have emphasized it. These rejects from Cushing's syndrome, together with other patients with some of their fea-

tures, have been nicknamed pseudo-Cushing's syndrome,[6] and more recently [11] have been placed in a group called the endocrine hypertensive syndrome.

Recognition of the syndrome discussed here is important for therapeutic reasons. The hypertension usually responds favorably to severe restriction of dietary salt,[6] and lesions in the ocular fundi may regress under this form of therapy. The lesions themselves have less serious prognostic significance than if found in a male patient with severe renal hypertension. It is possible that many reports of spontaneous regression of exudative and hemorrhagic lesions in ocular fundi may be based on similar cases.

Is the syndrome merely the chance occurrence of obesity in women with hypertension or the development of hypertension in obese women? We do not believe so, although insufficient attempt has been made to discover how many otherwise similar women are normotensive. The distinguishing features are characteristic enough for ready identification. The presence of hypertension may often be suspected by inspection, history of menstrual disturbances and rapid gain in weight. The low electrolyte values in sweat are not found in other types of hypertension, or in normotensive obese women without the other manifestations. The patients who state that they have always suffered from obesity may comprise a separate category from those who have gained weight rapidly, but the findings are as yet inconclusive to differentiate them.

The pathogenesis and etiology of this syndrome are obscure. A hereditary factor may predispose to hypertension of this variety, just as it does to others, and psychologic disorders may contribute. The pathways by which hypertension is initiated, however, may differ from those in the neurogenic and renal types. As yet we have only suggestive evidence for this hypothesis: (1) Sodium and chloride are handled differently, there being a definite tendency toward retention. (2) The response of the blood pressure to single injections of desoxycorticosterone acetate is magnified and prolonged.[23] (3) The hypertension responds favorably and often dramatically to restriction of salt.[6] (4) The response of the blood pressure to injected tetraethylammonium ion may be less than is usually seen in neurogenic hypertension. (5) The induction of the "diencephalic" blush by intradermal histamine is usually absent. (6) Adrenal cortical hyperplasia has been universally found so far.

The effects of hypertension on the vascular system also appear to be different. Nephrosclerosis is apt to be less severe than the history and level of the blood pressure would indicate. Signs of renal damage, such as diminished renal function and albuminuria, may be completely absent for many years. The clearance of urea and the excretion of phenol red may be supernormal, a surprising finding. At autopsy, renal vascular damage may be less severe than one would suspect from the degree and duration of hypertension; it may even be absent. While these clinical impressions are each

difficult to evaluate, taken together they form an imposing array worthy of more thorough investigation.

Russi et al.[24] examined 9,000 autopsy records and found 131 cases of adrenal cortical adenoma. Hypertension was five times more common in these than in the remainder of their cases. They also noticed that the degree of nephrosclerosis was less than would have been expected. The presence of obesity was not recorded. The incidence of tumors (1.45 per cent) compares favorably with the 1.75 per cent found in our series of 4,000 autopsies.

Summary

A syndrome found in hypertensive women characterized by central obesity (usually occurring rapidly), menstrual irregularities or gynecologic disturbances, and low sodium chloride concentration in sweat was described. The possible pathogenesis of this syndrome and its other distinguishing features were discussed.

Case Reports

Case 5. A 30 year old Negro woman first came to the out-patient department in 1946 complaining of shortness of breath and discomfort in her abdomen of three months' duration. Her father had died at 62 of dropsy, her mother at 43 after an operation on a gastric tumor when the patient was 20 years old. She has four sisters living and well; one exhibits central obesity, hirsutism, irregular menses and hypertension of 200 mm. Hg systolic and 130 diastolic. The patient had been slightly stout as a young girl but after her marriage at age 20 she suddenly gained 60 pounds in one year, and from then slowly gained 120 pounds in 10 years until she reached 291 pounds. Her menses were irregular and scanty for six years, sometimes occurring only once or twice a year, but since her marriage they have occurred every 18 to 28 days and last two days. She experienced attacks of blurring of vision and severe frontal headaches both at the beginning and at the end of her menses. Hypertension first appeared at the age of 26. She was placed on a diet and in three months lost 20 pounds. While stooping over a bathtub she suddenly experienced very severe generalized headache, dizziness and vomiting which progressed to semiconsciousness, and her neck became stiff.

On examination in November, 1946, her systolic blood pressure was 220 mm. Hg and her diastolic 130. She was extremely obese, with the exception of her lower legs and lower arms, which were practically free of fat. Her height was 64 inches and her weight 268 pounds. Her thighs and upper arms were enormous. She exhibited a "moon face," a "buffalo hump" and a very stiff beard which required shaving every three days. There were excess hair on her chest and a masculine distribution of hair on the abdomen. The fundi showed papilledema, arteriovenous compression and many exudates but no hemorrhages. The heart was enlarged to the left. Neurologic examination was consistent with subarachnoid hemorrhage, and xanthochromic spinal fluid under increased pressure with crenated red blood cells was found. Nonprotein nitrogen in the blood was 16 mg. per cent; blood count and urinalysis were not remarkable. Electrocardiogram revealed "coronary" type of myocardial damage and left axis deviation.

In the hospital the patient's condition improved rapidly. On a diet restricted as to salt her blood pressure fell to normal levels. After discharge she reduced her weight from 265 to 244 pounds. Her blood pressure rose to about 200 systolic and

120 diastolic; she was unable to keep to her diet. On re-admission to the hospital in October, 1947, her systolic pressure was 215 and her diastolic 140 mm. Hg. There were many pale striae about the arms, back, buttocks and thighs, and a pendulous abdomen and breasts. The ocular fundi now showed marked "silver wiring" and arteriovenous nicking and spasm. The heart was enlarged to the left and there was a loud, harsh, low-pitched systolic murmur heard over the precordium. There was no polycythemia or albuminuria. Plasma cholesterol was 210 mg. per cent. Blood chlorides remained from 109 to 113 except on a diet low in salt, when they fell to 99 mEq. per liter. Blood sodium was 142 mEq. per liter. There was no evidence of carbohydrate disturbance. The maximal specific gravity of her urine was 1.026. She was able to excrete 20 per cent of injected phenol red in 15 minutes and 55 per cent in two hours.* Urea clearance was 139 per cent of normal. Urinary sodium pregnanediol glucuronidate was 13 mg. in 24 hours, which is normal or slightly low. The 17-ketosteroid excretion was 3.3 mg. for 24 hours, a low value. The "Soffer" test for Cushing's syndrome revealed that the injection of DOCA caused increased excretion of intravenously injected salt, reportedly indicative of Cushing's syndrome.† Six weeks later there was decreased excretion of salt after administration of DOCA, a normal result. The abnormal response on the first test was probably due to concurrence of menses. Basal metabolic rate was normal. Electrocardiogram showed myocardial damage of a coronary type and left axis deviation. Retrograde pyelography disclosed no abnormalities. Her blood pressure fell when salt was restricted and rose rapidly when salt was added to her diet. When DOCA was injected intravenously the patient sustained a marked elevation in blood pressure which remained for 48 hours. In February, 1950, she was re-admitted for reëvaluation of possible endocrine factors of her hypertension and also because of acute gastroenteritis. Her blood pressure then was only 160 systolic and 102 diastolic. She was very obese, and was now shaving daily. The many striae on the abdominal wall were faintly bluish, rather than pale, as previously. There was a definite nuchal bony ridge with slight enlargement of the skull, but no evidence of acromegaly. There was no edema. The legs were still thin. The only alterations found were in the plasma cholesterol, now 108 mg. per cent. Sweat sodium concentration was very low, being 4 mEq. per liter. Blood sugar levels were sensitive to 1/40 of a unit of insulin per kilogram injected intravenously. The patient was given 1,040 units of roentgen therapy through three ports to the pituitary gland, without noticeable benefit. In 1951 she developed precordial pain, dyspnea on exertion and, occasionally, ankle edema. She became very weak. In the ocular fundi white areas of exudate developed, with occasional hemorrhages but without papilledema. Albuminuria appeared. Left pleural effusion and pulmonary congestion occurred. Only 10 per cent of phenol red was excreted in 15 minutes. Urinary excretion of corticoids and 17-ketosteroids was at normal levels, of sodium pregnanediol glucuronidate was 16 mg. in 24 hours, and of dehydroisoandrosterone was within normal limits. During the ensuing year progressive signs of cardiac decompensation appeared, and the patient was admitted for the sixth time to the hospital in March, 1952. She was dyspneic, orthopneic and edematous. The ocular fundi showed considerable papilledema, hemorrhage and exudate. The liver was enlarged and venous pressure elevated to 287 mm. of saline, with circulation time from arm to tongue of 37 seconds. Contrast x-ray photographs failed to demonstrate enlarged adrenal glands. One month after admission, bilateral almost total adrenalectomy was performed in two stages. The pathologic findings

* Renal plasma flow estimated from the clearance of para-aminohippurate was 512 c.c. per min., glomerular filtration rate from that of mannitol 118 c.c. per min. and filtration fraction .235.

† Soffer found that desoxycorticosterone acetate caused increased renal excretion of injected sodium chloride in Cushing's syndrome; in subjects with normal adrenal glands, retention is the rule.[27]

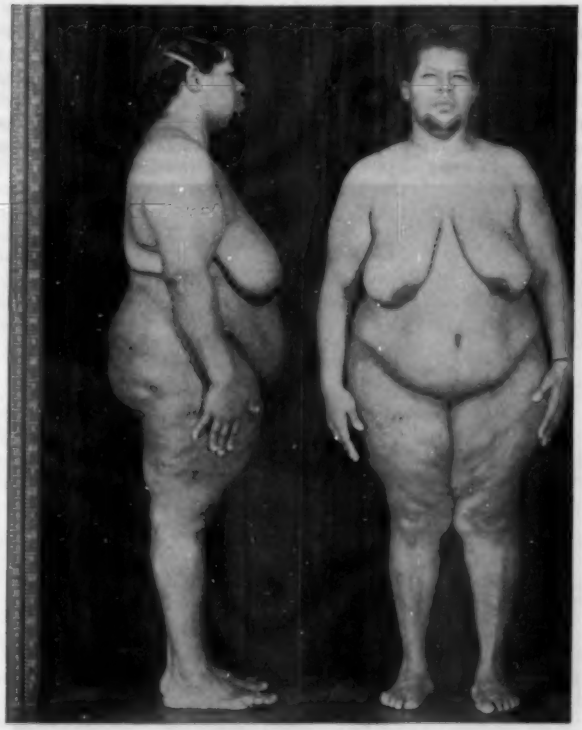

FIG. 1*A*. Body habitus of case 5. Note the beard, buffalo hump, panniculus and absence of fat on the distal extremities. Body weight, 234 pounds.

were cortical adenoma of the left adrenal gland and cortical hyperplasia of the right. Her systolic pressure fell from 210 to 160 and her diastolic from 140 to 110. On therapy with cortisone, plasma electrolytes remained within normal limits, but 12 days following operation her systolic pressure was 220 and her diastolic 140. The urinary excretion of 17-ketosteroids was 3.2 mg. per cent and of corticoids .8 mg. per cent. An eosinophil count showed no cells in the fasting preparation. Although the ocular fundi improved considerably and her weight fell to a low of 176 pounds she gradually gained again; at the time of writing she weighs 200 pounds and remains hypertensive, with a systolic pressure of over 200 and diastolic of over 130 mm. Hg (figure 1) except when taking 1-hydrazinophthalazine (Apresoline) and reserpine which cause her blood pressure to fall to normotensive levels.

Comment: The case is classed as an endocrine hypertensive syndrome with signs of adrenal cortical hyperactivity and adenoma and hyperplasia of both adrenal glands. Almost total adrenalectomy caused no eventual change in the level of blood pressure. This is an extreme example of the endocrine hypertensive syndrome. It is possible that other endocrine organs are disturbed.

Case 6. A 38 year old woman was of normal weight until the age of 33, when sudden amenorrhea appeared; within a year she gained 40 pounds, from a weight of 160, and eventually reached a maximum of 224 pounds. Her menarche had occurred at the age of 13; the menses had appeared regularly every 28 days, lasting seven days, with no clots, and were of only moderate quantity. She had had one pregnancy with a normal delivery. Two years after the obesity and amenorrhea developed, at the age of 35, an enlarged ovary was removed which contained a Leydig cell tumor.

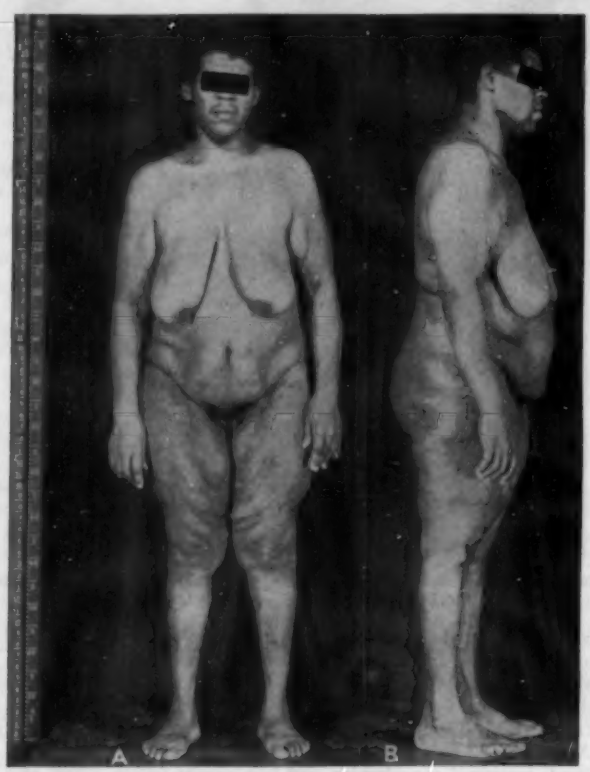

FIG. 1*B*. Case 5, body weight, 176 pounds, three months after subtotal adrenalectomy. At no time was this patient considered to exhibit Cushing's syndrome; there was no osteoporosis, no disturbance of carbohydrate metabolism, and no purplish striae.

Hypertension began at the age of 36. She bruised easily, enjoyed salty food and drank much water. She had extreme difficulty in losing weight; there was a tendency to edema of the ankles. On examination her blood pressure varied from 190 to 160 systolic and 130 to 100 diastolic. There were pale or faintly bluish striae on the upper arms, thighs, flanks, buttocks and abdomen. She had a ruddy moon-shaped face. Her breasts were large and pendulous, and the abdomen was protuberant and obese. There was hirsutism with a male distribution on the abdomen, and excess hair on the chin, upper lip, chest, arms and legs. There was acrocyanosis,

the arms and legs becoming spotted and mottled when dependent. There was acne on the back, chest and face. There was moderate kyphosis. The patient was round-shouldered. The clitoris was definitely enlarged. There was no glycosuria, but a fasting blood sugar of 87 mg. per cent rose to 181 in 60 minutes and 195 in three hours after oral ingestion of glucose. The plasma chlorides were 111 mg. per cent. The sella turcica was normal in x-ray photographs. There was considerable increase in the urinary excretion of 17-ketosteroids and of sodium pregnanediol glucuronidate, which were measured repeatedly. The red blood count was 5.8 million cells per cubic millimeter, with 16 gm. per cent of hemoglobin. Her kidneys could concentrate urine to a specific gravity of 1.022; there was no albuminuria and no glycosuria. Electrolytes in the blood were within normal limits. In the hope of suppressing adrenal function she was given daily injections of cortisone for a month. The only change appeared to be an increase in nervousness, but her elevated blood pressure was abolished. Considerable edema of the ankles appeared. Later irradiation of the pituitary caused no apparent changes. She was re-admitted in March, 1952. It was considered that she suffered from borderline diabetes, adrenogenital syndrome, hypertension and central obesity, all beginning with amenorrhea which had started four years previously. Surgical exploration revealed a benign adenoma 7 cm. in diameter in the left adrenal cortex, which was removed. The changes noted in the subsequent six months were loss of hirsutism, loss of 60 pounds in weight from a maximum of 225 pounds, decreased appetite, resumption of regular menses, increase in muscular strength, disappearance of edema of the ankles, a fall in blood pressure to normal levels, and disappearance of nocturia.

Comment: The endocrine hypertensive syndrome with virilism and diabetes was associated with a benign adrenocortical adenoma. Removal resulted in disappearance of symptoms and signs of adrenal cortical overactivity.

Case 7. A 41 year old woman was first seen in the out-patient department in 1943 because of edema of the legs following the bite of a scorpion. At that time she was obese, weighing 219 pounds; her systolic blood pressure varied from 145 to 110 mm. Hg and her diastolic from 95 to 76. Her cardiovascular status was considered as normal; her urine showed no abnormalities. She was next examined in 1947, four and a half years later; she then weighed 210 pounds and her systolic pressure was 260 and her diastolic 150 mm. Hg. There was no hypertension known in nine siblings, but her maternal grandfather had died of apoplexy. The mother and one sister are stout, particularly about the hips. Her menses began at the age of 12, were regular, lasted about a week and occurred every 28 days; they were quite scanty and were accompanied by pain in the left lower quadrant. She became pregnant 11 times and had 10 living children. She weighed 150 pounds at the age of 20 and gained none until 29 when, after her fifth pregnancy, she suffered an attack of puerperal sepsis; the following year she rapidly gained 60 pounds in weight. Her maximal weight was 230 pounds; she had weighed about 220 pounds for at least 10 years. She claimed that her appetite was not excessive, but she had great difficulty in losing weight. Her obesity was always central in type. At the age of 43 her systolic blood pressure was found to be 190 mm. Hg, which fell to 140 during treatment with "tablets." Two months before admission to the hospital she developed severe headaches which recurred almost daily, dyspnea at night and orthopnea. She complained of frequent episodes of pain in her eyes, with severe aching and blurring of vision. There was no history of diabetes.

On examination in October, 1947, her systolic pressure was 224 mm. Hg and her diastolic 140. She was greatly overweight, with the obesity confined to the trunk and proximal parts of the extremities. There were large pendulous breasts

and a thick panniculus. The face was moon-shaped. The distal extremities were not involved in the accumulation of fat. Her voice was a little hoarse. The clitoris was not enlarged. There were many pale striae on the abdomen and buttocks. There was no hirsutism. In the ocular fundi were scattered areas of exudate and a few fresh hemorrhages. Her heart was not enlarged. There was no polycythemia.

There was a trace of albumin in the urine; nonprotein nitrogen in the blood was 19 mg. per cent. An oral glucose tolerance test revealed fasting blood sugar of 119 mg. per cent which rose to 174 in half an hour, 243 in one hour, 225 in two hours, and 158 in three hours. Plasma cholesterol was 283 to 310 mg. per cent. Plasma sodium was 144, chloride 105, and carbon dioxide combining power 19.9 mEq. per liter. The patient was able to excrete 30 per cent of injected phenol red in 15 minutes and 65 per cent in two hours; the clearance of urea was 98 per cent of normal.* Her kidneys were able to concentrate urine to a specific gravity of 1.024. Electrocardiogram showed an abnormal form of ventricular complex. Electroencephalogram displayed a fast irregular rhythm with asymmetry of amplitude suggestive of suppressed cortical activity in the left temporal region. Basal metabolic rates were minus 9, minus 4, plus 6 per cent of normal. Urine specimens for glucose revealed an excretion of 0 to 3 gm. per 24 hours. X-ray of the chest showed cardiac enlargement and lengthening of the aorta; there was no osteoporosis. Pyelograms after intravenous injection were normal. During a sodium amytal release test her systolic pressure dropped from 200 to 138; her diastolic was unchanged. The intradermal histamine test was negative. "Cold pressor test" caused a rise in systolic and diastolic pressure of 30 mm. A "Soffer" test for Cushing's syndrome was performed just prior to her menses; the urinary excretion of chloride increased 60 per cent following the injection of desoxycorticosterone acetate, which supposedly indicates Cushing's syndrome.[27] The test, however, was repeated at a different period in the menstrual cycle, when a 39 per cent decrease in chloride excretion occurred—a normal result. She was given 5 mg. of DOCA twice a day for 10 days and became definitely worse, with increase in nervousness, pain in her eyes and hypertension. She was given a diet containing 800 calories and lost 30 pounds in weight in three months.

She was re-admitted to the hospital in January, 1949. During the intervening period of a year she had been doing fairly well on a diet containing 1 gm. of salt, but she was unable to lose weight. Her systolic pressure was 200 and her diastolic 100 mm. She was still markedly obese. In the left retina was an old exudate. Otherwise the physical examination was unchanged. Her kidneys were able to excrete 30 per cent of injected phenol red in 15 minutes and 64 per cent in two hours, and to concentrate urine to a specific gravity of 1.030. Clearance of urea was 105 per cent of normal. Oral glucose tolerance test again revealed a diabetic curve without glycosuria, but less marked than the previous one. Sodium concentration of sweat was 22 mEq. per liter, a low value. The patient was given a diet containing 800 calories and 0.5 gm. of salt; fluids were limited to 1,500 c.c. per day. On this regimen her blood pressure dropped markedly and was maintained at about 140 to 150 mm. systolic and 90 to 100 diastolic. She became very comfortable. After two months the amount of salt in her diet was increased to 16 gm. per day; she became mildly edematous, felt uncomfortable, and exhibited decrease of urine volume lasting about 10 days.† Following discharge from the hospital her blood pressure rose when salt was taken, her diastolic being about 110 and her systolic 200 to 230 mm. Hg, although she had maintained a weight of about 175 pounds (figure 2).

* Renal plasma flow estimated from the clearance of para-aminohippurate was 538 c.c. per minute, glomerular filtration rate from that of mannitol 77 c.c. per minute, and filtration fraction .142.

† This patient was studied by Daughaday and MacBryde who found a "remarkable carry-over of sodium conservation which produced a sodium retention far in excess of any possible deficit accrued by sodium restriction" when changing suddenly from an intake of 3 mEq. to 205 mEq. per day.[28]

Comment: An endocrine hypertensive syndrome was associated with a diabetic element in a woman whose sudden weight gain occurred after childbed fever. She did not have the irregular menses so common in other cases. Pathologic changes in the adrenal cortex have not been demonstrated.

Case 26. A 37 year old housewife complained of nausea, vomiting and twitching for two weeks. She had become obese after the menarche at age 11, and the obesity had increased in the last 10 years. She had also for many years exhibited hirsutism, which had increased during the last two years. Her menses were very irregular and unpredictable; at the age of 30 there had been one pregnancy which terminated in a miscarriage. Three years before admission a physician discovered that her systolic blood pressure was 230 to 240 mm. Hg; it fell moderately with the loss of

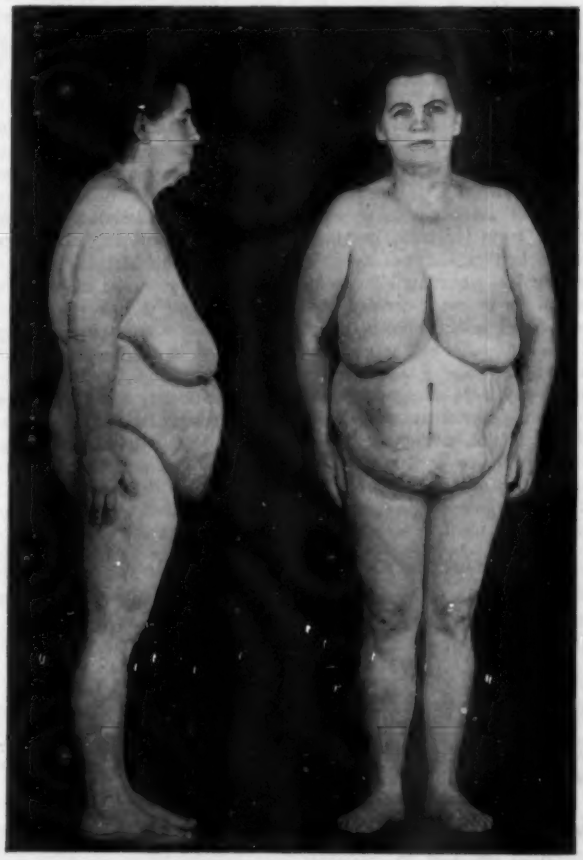

FIG. 2. Body habitus of case 7 after loss of 20 pounds. Note the buffalo hump, panniculus, central obesity. There was a disturbance of carbohydrate metabolism. The central obesity pictured here is typical of that characteristic of the endocrine hypertensive syndrome.

weight accompanying a reducing diet. She lacked energy and complained of weakness but had no other symptoms. Three months before admission she developed an upper respiratory infection followed by paroxysmal nocturnal dyspnea. Orthopnea, wheezing, visual disturbances and loss of vision in the right eye became manifest; there were also confusion, delirium and hallucinations. On the day before admission nausea and vomiting increased and gross muscular twitching began.

On physical examination her systolic pressure was 260 and her diastolic 160 mm. Hg. She showed marked central obesity and hirsutism, with a beard and mustache. In the ocular fundi were papilledema, vascular spasm, and fresh and old hemorrhages and exudate. The heart was enlarged and there was a harsh, loud systolic murmur at the apex. Urine showed 4 plus albuminuria with occasional granular and hyaline casts, red blood cells and white blood cells in the sediment. On culture of the urine a colon bacillus grew; the infection was treated. Nonprotein nitrogen in the blood was 64 mg. per cent, carbon dioxide combining power 33.4 mEq. per liter, chlorides 90, sodium 138 and potassium 3.5 mEq. per liter. Levels of calcium and phosphorus were within normal limits. Electrocardiogram showed the pattern of left ventricular enlargement. Her red blood count was repeatedly over 6 million per cubic millimeter, sometimes as much as 6.6 million, with more than 16 gm. of hemoglobin. On lumbar puncture, pressure of the spinal fluid was 350 mm. of water, with a protein content of 83 mg. per cent. Neither glycosuria nor hyperglycemia was noted; there was no increase in the urinary excretion of 17-ketosteroids or corticoids. Renal function was considerably reduced. Osteoporosis was not noticed in x-ray photographs. X-rays of the skull were normal. Wide variations in the sodium concentration of plasma occurred, from 155 mEq. per liter to 123 mEq. per liter; attempts were made to correct the deficit or the increased concentration, with little success. Her blood pressure remained at very high levels until her dietary intake of salt was severely restricted, when there was a decided and significant fall to lower levels. There appeared to be a direct relationship between the sodium concentration in the plasma and the level of blood pressure. The nonprotein nitrogen in the blood fell to 45 mg. per cent but rose slowly and gradually until uremia developed and the patient died. Findings at autopsy were malignant nephrosclerosis, obesity and cardiac hypertrophy, predominantly left ventricular, with the heart weighing 510 gm. There was a small adenoma of the cortex of the left adrenal gland. Moderate arteriosclerosis of the aorta, coronary arteries and renal arteries, and slight arteriosclerosis of splenic, superior mesenteric and hepatic arteries were also demonstrated. There were cholesterosis of the gall-bladder, an accessory left renal artery, focal hyperplasia in the right kidney and focal hyperplasia of the endometrium.

Comment: The endocrine hypertensive syndrome was associated with an adenoma of the cortex of the left adrenal gland, hirsutism, irregular menses and central obesity of long duration, complicated by uremia secondary to malignant hypertension.

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THE CLINICAL USE OF THE EXSUFFLATOR ATTACHMENT FOR TANK RESPIRATORS IN POLIOMYELITIS*

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Mortality in acute poliomyelitis is almost entirely limited to those cases having respiratory or bulbar paralysis, and particularly to those having a combination of both. Although cardiovascular collapse, hyperthermia and gastrointestinal hemorrhage may occur, the major complications are respiratory, particularly when paralysis of respiratory muscles is complicated by an inability to swallow or phonate. Severe anoxia and retention of carbon dioxide may develop and be further complicated by atelectasis or infection. The mechanism of coughing will normally prevent the development of these complications, but this requires not only muscles of active expiration but also the ability to build up a pressure behind the closed glottis for explosive expiration. Of all the measures used in the treatment of these desperately ill patients—postural drainage, aspiration of the pharynx, oxygen therapy, antibiotics, tracheotomy and bronchoscopy—only bronchoscopic aspiration will overcome with any certainty the accumulation of secretions which result from the patient's inability to cough.

The exsufflator attachment for tank respirators developed by Barach and his colleagues [1, 2, 3] has been reported to remove bronchial secretions effectively in various conditions, including poliomyelitis, where there is an ineffectual cough.[4] A beneficial effect has also been noted in the management of respiratory acidosis in pulmonary emphysema.[5] The purpose of this paper is to report the clinical results of exsufflation in 12 cases of poliomyelitis with respiratory complications.

Methods

The *exsufflator* consists essentially of a vacuum cleaner motor and a butterfly valve which is attached to the port of a standard Emerson respirator. The machine is quite mobile and can be attached to a respirator in a minute or two or left attached to the respirator when not in use. With the valve closed, the motor blower develops a high negative intra-tank pressure. At the height of inspiration the butterfly valve suddenly opens, allowing an almost instantaneous return to atmospheric pressure in the tank. The frequency, duration of inspiration and depth of inspiration can be regulated easily. We have used it at a frequency of 9 to 12 per minute with an in-

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spiratory phase of two seconds at a pressure of 35 to 45 cm. water for periods of 10 to 30 minutes, repeated when necessary.

The *patients* used in this study all required treatment in respirators. The first eight were all the acute cases with evidence of respiratory obstruction encountered since obtaining the exsufflator. All eight had involvement of the lower bulbar nuclei as well as severe involvement of respiratory muscles. The remaining four cases were over the acute stage of polio but were still in respirators when episodes of respiratory obstruction developed.

The exsufflator was applied to relieve cyanosis and obstruction to the airway in patients with or without tracheotomy. All but one had developed cyanosis in spite of controlled respiration in tank respirators, posturing, frequent aspiration of the pharynx and the vigorous use of oxygen therapy. Obstruction to the airway was characterized by distress. In many, palpable rhonchi were noted over the chest and bubbling râles could be heard over the trachea while the patient was in the respirator. There was often an associated rise in blood pressure and pulse rate.

Results

The results can best be assessed from the following brief case reports. These notes have been limited to respiratory complications only. Some of these cases are more fully reported elsewhere.[6]

The exsufflator was of greatest help in the management of purulent tracheitis, particularly after tracheotomy. This is well illustrated in case 1, who had had a tracheotomy performed shortly before the exsufflator became available. In cases 2–8 it was hoped that the use of the exsufflator would obviate tracheotomy. The remaining four cases illustrate its usefulness in chronic poliomyelitic patients in respirators. The exsufflator was not available during the acute illness in these four patients.

Case Reports

Case 1. A 24 year old female was admitted with a rapidly ascending paralysis involving all spinal segments and the lower bulbar nuclei. She was placed in a respirator within a few hours of admission. On the third hospital day she became cyanosed, and a tracheotomy was performed. A moderate amount of thick purulent secretion was immediately aspirated through the tracheotomy tube, with marked improvement in cyanosis. From the fourth to the twenty-second day there were frequent bouts of severe respiratory obstruction, sometimes relieved by deep tracheal aspiration but requiring bronchoscopic aspiration of thick tenacious secretions on 22 occasions. Often the secretions were inspissated to solid masses plugging the main bronchi and requiring removal by forceps.

On the twenty-second hospital day the exsufflator was first used for 10 minutes. A large amount of thick yellow pus and small solid clots were aspirated from the upper trachea. The signs and symptoms of respiratory obstruction were as quickly and completely relieved as by bronchoscopy on previous occasions. For the next 10 days the exsufflator was used two or three times a day, and for the next five days once a day, with removal of much mucopus on each occasion (figure 1).

By the thirty-eighth hospital day the airway remained clear of excessive secretions, and the patient had no further episodes of obstructive dyspnea.

Case 2. This 34 year old male had been ill for three days prior to admission. He was unable to phonate and had progressive weakness of his arms and respiratory muscles. Respirator treatment gave considerable relief but the paralysis progressed. On the third hospital day he became slightly cyanosed in the respirator. Tracheotomy was delayed and exsufflation applied for 15 to 20 minute periods four times that day, though with little noticeable change. Early on the fourth day he became quite cyanosed and had severe respiratory distress. Exsufflation for 20 minutes raised a small amount of secretion and the distress was temporarily relieved. While the patient was being prepared for tracheotomy the exsufflator was used again for 30 minutes, with considerable relief of cyanosis and production of an appreciable amount of mucopus.

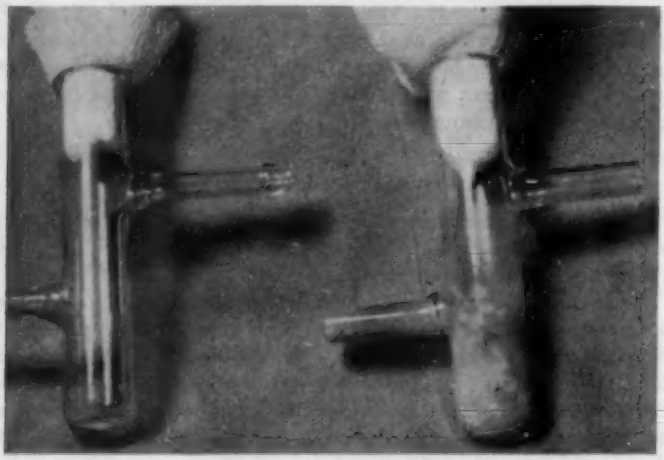

FIG. 1. *Case 1* complained of obstructive dyspnea. Fifteen minutes of deep tracheal aspiration produced only a negligible amount of secretion and no relief. After 10 minutes exsufflation, a large quantity of thick pus was aspirated from the upper trachea.

Immediately after tracheotomy approximately 50 ml. of mucopus were aspirated from the trachea, with marked improvement in ventilation.

For the next eight days the exsufflator was required three to four times daily, each time with production of pus which was then aspirated through the tracheotomy. The patient's respiratory muscles began to improve and soon he was able to cough up the still profuse mucopurulent secretion without assistance.

Case 3. A 15 year old male was admitted with muscle weakness appearing after a three-day illness. Temperature rose to 105° F., and the paralysis gradually increased; he became confused and disoriented, and on the third hospital day he required treatment in a tank respirator. He continued to deteriorate and by the fourth day was unable to swallow saliva. Tracheotomy was considered but prophylactic use of the exsufflator once or twice a day raised small amounts of mucoid secretion and maintained a clear airway. By the seventh day he began to improve. Consciousness gradually cleared and swallowing returned. By the fortieth hospital day he was able to remain out of the respirator entirely, although there was considerable residual paralysis.

Case 4. A 52 year old male who had been ill for three days was admitted with fever, nausea and vomiting, and paralysis of the respiratory muscles, the sternomastoids and the left palate. Coarse rhonchi were heard over the entire chest. Respiratory distress persisted in the respirator. Exsufflation produced about 40 ml. mucus from the trachea, with relief of distress, but the procedure was discontinued after five minutes because of increased nausea. On the third hospital day he became cyanosed and very confused in the respirator. Heart rate rose to 140 per minute. Exsufflation produced some mucoid sputum and much relief in dyspnea, color and state of consciousness. Two hours later he again became distressed, cyanosed and confused, and again there was some relief with exsufflation. A tracheotomy was performed shortly afterwards. Approximately 20 ml. of yellow thick pus were aspirated from the trachea through the wound, with marked improvement in mental signs and in his color.

From the fourth to the twelfth hospital day he remained acutely ill, with episodes of confusion and delirium. He was exsufflated once or twice a day during this week,

FIG. 2. *Case 4.* Photograph of a large solid plug of mucopus coughed from the tracheotomy wound by the exsufflator.

whenever the airway seemed partially occluded and when repeated deep tracheal aspiration had failed to relieve the obstruction. On each occasion moderate amounts of thick yellow pus were brought into the upper trachea in reach of the suction catheter.

By the twelfth day the tracheal secretions were very thick and tenacious. Exsufflation delivered a large firm plug of mucopus into the tracheotomy wound (figure 2). However, later the same day repeated periods of exsufflation failed to relieve the airway obstruction for longer than a few minutes. Bronchoscopy was performed and a moderate amount of thick pus was aspirated from the trachea. On the fourteenth and fifteenth hospital days he again required bronchoscopic removal of pus and plugs from the trachea and right main bronchus, after deep tracheal aspiration and exsufflation had failed to relieve the obstruction.

By the sixteenth day the tracheal secretions became liquid and could be removed by aspiration alone. Respiratory function and swallowing began to return, and a month later he was out of the respirator and the tracheotomy cannula was removed.

Case 5. A 31 year old female was admitted after one week's illness with early paralysis. By the third hospital day she required a respirator. However, there was

further extension of the paralysis and on the fifth day moderate respiratory obstruction developed. This was partially relieved by aspiration of thick purulent blood-tinged secretion. Exsufflation gave further relief. On the eighth day the patient became unconscious and stopped swallowing. Cyanosis developed and, as it was not relieved by exsufflation, a tracheotomy was performed. Although no secretion was aspirated from the trachea, the cyanosis improved.

On the tenth hospital day bronchoscopy was performed after the airway became obstructed. Considerable thick mucus and blood clot were removed from the trachea and main bronchi with forceps. Ventilation was much improved. The next day the patient regained consciousness. In the following 16 days she was bronchoscoped once and sometimes twice daily for the relief of dyspnea, which was unrelieved by aspiration or exsufflation. On one occasion exsufflation for a partially obstructed airway made the patient suddenly worse. The bronchoscope was immediately passed and the trachea found to be completely obstructed with very thick secretions.

From the eighteenth day dyspnea and cyanosis were relieved less and less by bronchoscopy, and even though a very high concentration of oxygen was delivered into the trachea the cyanosis gradually became worse. Fever increased to 102° to 103° F. and the patient died on the twenty-sixth hospital day. Postmortem examination of the chest revealed bilateral pleural effusions and extensive pneumonia in both lungs.

Case 6. A 24 year old male was admitted on the fourteenth day of his illness with beginning paralysis which increased to the point of requiring the use of a respirator. By the third hospital day he was noisy and irrational and could not swallow. He was mildly cyanosed for several days, and tracheotomy was seriously considered. On the fifteenth hospital day he became pale, clammy, cyanosed and unconscious. Exsufflation for 15 minutes raised a considerable amount of mucoid secretion to the pharynx which was cleared by suction. His color improved and consciousness was restored, but he remained confused. He had similar episodes on three occasions during the following week, each time with some improvement in ventilation following exsufflation and the aspiration of mucopus from the pharynx. During exsufflation this patient's blood pressure dropped to below 100 mm. Hg but promptly returned to normal after the treatment.

By the third week his mental state had returned to normal and voluntary respirations gradually returned.

Case 7. A 34 year old male was admitted in a portable chest respirator with a nine-day history of fever and progressive paralysis which involved the respiratory muscles. Deterioration continued, and by the next day he was delirious and unable to cough or swallow. Sudden severe cyanosis was relieved by exsufflation, although only a small amount of thick secretion was aspirated from the pharynx. This temporary respite was consolidated by tracheotomy, when a large amount of yellow pus was aspirated through the wound. For the next few days exsufflation raised large amounts of pus and an occasional tenacious plug of mucopus into the upper trachea, in reach of the suction catheter. After one of these treatments bronchoscopy was performed as it was considered unlikely that the exsufflator alone could clear adherent plugs from the bronchi. The bronchial tree was practically clear of secretions.

Over the next few weeks improvement was steady, and he was completely out of the respirator by the eighth hospital week. The tracheal cannula was removed a few days later.

Case 8. A 27 year old male was admitted in the acute stage of his illness with generalized weakness and dyspnea. A tank respirator gave some relief, but an hour later he was severely cyanosed. Repeated exsufflation gave some relief of distress and cyanosis. Tracheotomy was performed 15 hours after admission. A large amount of creamy pus was aspirated from the trachea, with relief of dyspnea and

cyanosis. For the next four days the airway was kept clear by exsufflation three to four times a day, with removal of large quantities of pus from the upper trachea.

During the next week the airway was kept clear by aspiration alone, but on the twelfth hospital day he was again distressed and obtained only temporary relief from exsufflation. Bronchoscopic aspiration removed much thick secretion from the trachea and left main bronchus, with relief of dyspnea. On the fourteenth day firm adherent plugs were removed from the trachea and both main bronchi by bronchoscopy after the exsufflator had failed to produce more than temporary relief. He was free of symptoms for 17 days but then developed fever and dyspnea. Ten milliliters of pus were aspirated from the upper trachea, with some improvement. Exsufflation for 15 minutes yielded an additional 20 ml. of pus, with considerably more relief of dyspnea. During this episode, which lasted three days, he was exsufflated once or twice a day with good results. The infection subsided with antibiotics.

Thereafter improvement was steady. The tracheal cannula was removed on the seventieth hospital day, by which time he was able to stay out of the respirator for several hours at a time.

On one occasion when this patient was acutely ill and unable to do without artificial respiration for more than a minute the motor of the respirator suffered a mechanical breakdown. The exsufflator was used as an auxiliary respirator for one and one-half to two hours while repairs were effected.

Case 9. A 25 year old female was admitted in August, 1952, in the acute stage of poliomyelitis, with severe paralysis of all spinal muscle groups and requiring treatment in a tank respirator. There was transient involvement of swallowing in the acute stage, but tracheotomy was not necessary. Improvement was slow but by the third month she was able to get along by using a chest respirator for only a few hours a day, although her vital capacity was only 350 ml.

Six months after admission she developed an acute rhinitis and laryngitis with fever and dyspnea. She was unable to raise sputum, and transferring her back to a tank respirator was of little help. Dyspnea increased and mild cyanosis developed. Exsufflation produced relief of dyspnea and cyanosis, and small amounts of sputum were coughed through the glottis. This was repeated three times during the next few days until the infection subsided.

Case 10. A 39 year old male was admitted cyanosed and unconscious. He was considerably improved in a tank respirator and with a tracheotomy, but was left with complete spinal paralysis and serious involvement of the lower bulbar nuclei. During the four weeks following admission he required 22 bronchoscopic aspirations to remove thick inspissated secretions from the trachea and main bronchi. The tracheobronchitis subsided, he had slow but incomplete return of swallowing, and the tracheotomy tube was plugged except during meals.

Five months after admission he developed a "cold" with acute tracheitis. Moderate amounts of thick secretions and a few small solid clots of mucopus were removed by deep tracheal suction. Two days later dyspnea unrelieved by aspiration was relieved by exsufflation, which yielded moderate amounts of secretion. The infection soon subsided and the airway subsequently remained clear.

Case 11. A 27 year old female was admitted in a portable respirator with fever and paralysis of recent onset involving all spinal groups and partially the left facial muscles. The acute illness rapidly subsided but left practically complete residual paralysis. After three months she was able to remain out of the respirator for 10 minutes at a time.

Four months after admission she developed an acute upper respiratory infection, with nasal discharge, dyspnea, tachycardia and fever. She was severely dyspneic if the respirator was opened for a minute. Exsufflation was used once or twice a day, with considerable relief of respiratory distress and production of moderate amounts

of thick yellow mucopus. More copious secretions were raised, with greater relief of dyspnea, by exsufflating the patient in the prone position with the head tilted down. These measures maintained a clear airway for approximately three weeks until the acute infection subsided.

Case 12. A 35 year old female was admitted in the acute stage with severe spinal and lower bulbar paralysis requiring treatment in a respirator. Tracheotomy was performed on the second hospital day. After a stormy three weeks, during which time she required bronchoscopic aspiration 17 times, the acute disease subsided and she remained well, although with marked residual paralysis. Her ability to swallow and phonate gradually returned, but her respiratory muscles remained completely paralyzed. After the tracheotomy tube was closed for a trial period, the cannula was removed.

The following day she was cyanosed and dyspneic. This was immediately relieved by exsufflation, with production of a moderate amount of thick mucoid sputum. The next day dyspnea and cyanosis were again relieved by exsufflation. Her subsequent course was uneventful.

Discussion

The case reports illustrate the respiratory difficulties encountered in patients who have an ineffectual cough. They also illustrate that the tank respirator with the exsufflator attachment has certain advantages over the standard tank respirator. These advantages warrant some comment, as do the limitations and disadvantages noted.

When a patient has combined respiratory and bulbar paralysis and cannot swallow or cough it is difficult to maintain a clear airway. We have tried to train patients to "cough" during the expiratory phase of the respirator cycle by closing the glottis at the height of inspiration. This is impossible in patients who are confused and irrational or who have laryngeal paralysis. At best this procedure produces a very ineffectual cough. Our previous experience with cases of combined respiratory and bulbar paralysis favors tracheotomy.[7] The hope that the exsufflator would obviate tracheotomy has not been sustained (cases 2, 4, 5, 7 and 8), although in cases 3 and 6 tracheotomy may have been avoided by exsufflation.

In spite of the use of antibiotics, the high humidity of inspired air, proteolytic enzymes and adequate hydration, purulent membranous tracheitis was a prominent feature in those cases with combined lower bulbar and respiratory paralysis. This may be aggravated by tracheotomy and repeated passage of a rubber catheter or bronchoscope. Although the acute tracheitis is usually self-limiting, lasting two to four weeks, we found frequent bronchoscopic removal of secretions a life-saving measure in many cases, before the exsufflator was available. In cases 1, 2 and 7 the exsufflator completely replaced bronchoscopy as a means of keeping the airway clear of thick tenacious secretions, although cases 4 and 8 each required bronchoscopy on three occasions. From our previous experience it is clear that the exsufflator spared these patients many bronchoscopic aspirations. In case 5 exsufflation was unsuccessful and repeated bronchoscopy was necessary.

Patients continuously in respirators, or those who have been left with marked limitation of respiratory reserve, have a good deal of trouble with

"minor" respiratory infections. Cases 9, 10 and 11 developed acute upper respiratory infections with marked respiratory difficulty. Had the exsufflator not been available they would probably have required repeated bronchoscopic aspiration. Case 11 might have required tracheotomy, as the episode of tracheobronchitis lasted three weeks.

It is often difficult to know when a patient who has had a tracheotomy and has considerable residual respiratory paralysis can safely have the cannula removed. Case 12 illustrates the danger of premature decannulation. This patient would have required bronchoscopy or re-opening of the tracheotomy if the exsufflator had not been successful in clearing the airway.

Even in cases in which the exsufflator failed to "cough up" secretions its use usually resulted in improved ventilation and relief of cyanosis. Although this relief was often sustained only while the exsufflator was used, it allowed tracheotomy or bronchoscopy to be converted from emergencies to planned procedures. Both bronchoscopy and tracheotomy require special skill and training, while exsufflation is a simple procedure which can be brought into use quickly by the house staff. A bronchoscope should, however, always be readily available. On one occasion (case 5) the exsufflator apparently moved thick secretions from the bronchi into the trachea, completely obstructing the airway, which then had to be cleared by emergency bronchoscopy.

Minor side effects were noted in cases 4 and 6. In the former exsufflation aggravated nausea, but as this subsided the machine was used to good effect. In case 6 a temporary drop in blood pressure was noted during exsufflation. This had no apparent ill effects.

When the exsufflator was first used on any patient who had been in a respirator for several weeks or months the resultant deep inspiration caused pain in the chest if a high negative intra-tank pressure was developed without a process of acclimatization. This is probably due to contractures of paralyzed muscles causing fixation of the chest wall, which may perhaps be prevented or corrected by intermittent deep breaths.[8] The use of the exsufflator for this purpose is currently under study.

The mechanical breakdown recorded in case 8 shows that the exsufflator is useful as an auxiliary motor for tank respirators. The control of inspiratory to expiratory ratio would be a useful feature on standard respirators. A prototype of a respirator operating on these principles is already being tested.[9]

Summary and Conclusions

The exsufflator attachment to the standard respirator is a valuable adjunct in the treatment of the respiratory complications of poliomyelitis both to increase effective ventilation and to clear secretions from the tracheobronchial tree.

In six cases with tracheotomy in the acute stage of the disease it successfully cleared the lower trachea and main bronchi of secretions which

could then be removed by suction through the tracheotomy. Although the exsufflator was not always successful in removing solid plugs of mucopus, it reduced the number of necessary bronchoscopic aspirations.

The exsufflator almost always reëstablished adequate ventilation in cyanosed and dyspneic patients. Although this relief was sometimes short-lived, it was found to be very useful in preventing prolonged periods of anoxia while preparing for tracheotomy or bronchoscopy, if these were indicated.

In two of seven patients the exsufflator may have obviated the necessity of tracheotomy.

In one patient the exsufflator increased nausea. In another it appeared to increase airway obstruction.

Patients who had been in respirators for some weeks found full inspiration with the exsufflator uncomfortable unless higher negative intratank pressures were approached gradually.

In case of mechanical breakdown of the tank respirator the exsufflator may be used as an auxiliary power unit.

ACKNOWLEDGMENT

We are greatly indebted to Dr. A. L. Barach for making the exsufflator available to us.

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EOSINOPHILIC GRANULOMA OF LUNG: REPORT OF THREE CASES*

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Eosinophilic granuloma of bone as a clinical entity was first delineated by Lichtenstein and Jaffe [1] in 1940. Their report was based on the case history of a four year old girl with a lesion of the femur, which was considered to represent a previously undescribed granuloma of bone containing many eosinophils. Otani and Erlich [2] described the same type of granuloma of bone and stated that its roentgenologic appearance simulated that of primary neoplasm. Farber [3] postulated that eosinophilic granuloma of bone, Hand-Schüller-Christian disease, and Letterer-Siwe disease are variations of the same entity. This was supported by Green and Farber's [4] study of 10 cases of lesions of bone, four single and six multiple, all occurring in patients under 12 years of age and identical to those described as eosinophilic granuloma. These cases varied pathologically from eosinophilic granuloma to lipogranuloma, closely resembling certain stages of Hand-Schüller-Christian disease. From these observations the authors concluded that eosinophilic granuloma is a variant of a process of which the clinical pictures of Hand-Schüller-Christian and Letterer-Siwe diseases are other examples, and they suggested the possibility of visceral lesions.

Engelbreth-Holm et al.[5] reported five cases of eosinophilic granuloma of bone in children presenting clinically, symptomatically and morphologically a gradual transition to the fully developed Hand-Schüller-Christian syndrome. Their cases presented single bone or multiple bone lesions, and in one instance multiple bone foci, diabetes insipidus, disturbance of growth and roentgenographic changes in the lungs. The osseous lesions proved pathologically to be those of eosinophilic granuloma, regarded by the authors as a single focus of Hand-Schüller-Christian disease often healing without becoming generalized.

Weinstein et al.[6] as well as Dixon [7] reported single cases of multiple skeletal lesions associated with pulmonary infiltrations. The bone lesions in both instances were revealed by biopsy to be eosinophilic granulomata. Similar cases were noted by Schuknecht and Perlman [8] and by Parkinson.[9] Farinacci et al.[10] observed two cases of diffuse pulmonary infiltration of clinically undetermined etiology which on biopsy of the lung were interpreted as eosinophilic granuloma. Neither case showed evidence of lesions elsewhere. These were apparently the first cases of histologically proved eosinophilic granuloma of the lung. McKay et al.[11] reported three cases of

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eosinophilic granuloma of the vulva. All of them had diabetes insipidus. Two patients had cranial lesions suggestive of Hand-Schüller-Christian disease, and one of these showed roentgenographically diffuse pulmonary infiltration.

Case Reports

Case 1. This 40 year old white male carpenter was hospitalized May 27, 1952, at the Veterans Administration Hospital, Oakland, California, with a history for one month of pain in the right posterior chest accentuated by coughing and sneezing. Tenderness developed in this area. A roentgenogram showed a destructive lesion of the right fifth rib posteriorly. This increased in size in two weeks. The patient had noted increasing fatigue for three or four years but no weight loss or other symptoms.

Examination revealed a patient who appeared in good general health. The abnormal finding was a tender area over the posterior portion of the fifth rib just medial to the scapula. A firm, slightly tender mass expanding the rib was palpated.

The erythrocyte count was 5.58 million and the hemoglobin was 102 per cent. The leukocyte count was 8,500, with 65 per cent polymorphonuclears, 4 per cent bands, 23 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. Urinalysis was normal, including a negative test for Bence Jones protein. Total blood proteins were 7.92 gm. per cent, with 5.56 gm. per cent albumin and 2.36 gm. per cent globulin. A Kahn test was negative. Blood calcium was 10.8 mg. per cent, phosphorus 3.4 mg. per cent, acid phosphatase 0.2 mg. activity, and alkaline phosphatase 1.9 mg. activity. Sputa were negative for acid-fast bacteria. Chest roentgenograms were negative except for a 1.5 cm. destructive lesion in the posterior part of the right fifth rib (figure 1). Intravenous pyelogram and roentgenographic studies of the upper gastrointestinal tract and a barium enema were normal. The sternal bone marrow was within normal limits. Bronchoscopic examination was negative. The destructive costal lesion was excised with a wide margin on June 5 under endotracheal anesthesia. Through the incision the lung was palpated and a 1 cm. peripheral nodule was found in the upper lobe. This was removed by wedge resection. Grossly it contained a central cavity. Frozen section preparations appeared to show an undifferentiated carcinoma with necrosis and acute and chronic cellular infiltration. The incision was then enlarged and the lung palpated carefully. Another smaller lesion was felt in the region of the excision but the remainder of the lung seemed normal. There were no palpable hilar lymph nodes. Only an upper lobectomy was performed because there was no evidence of disease in the rest of the lung or mediastinum. Pathologic study of permanent sections of the lobe did not confirm the impression from the frozen section of undifferentiated carcinoma. The final tissue diagnosis was eosinophilic granuloma. Convalescence was uneventful.

The patient one year postoperatively is working and is asymptomatic. Physical examination is negative. Chest roentgenograms show no change, and a roentgenographic bone survey is negative.

Pathology: A destructive lesion involved the rib over a distance of 3.0 cm. The cortex and marrow cavity were replaced by a moderately firm gray-white tissue with poor demarcation. The lesion involved the adjacent soft tissues for a distance of 0.5 cm. Microscopic sections revealed destruction of bone and its replacement by a granulomatous tissue composed predominantly of histiocytes and eosinophils. Segmented eosinophils were more numerous than younger forms. There was a loose fibrovascular stroma which contained small numbers of lymphocytes and neutrophilic polymorphonuclear leukocytes. The cytoplasm of the histiocytes was abundant, and

it varied from pale and foamy to pink and homogenous. There were occasional larger multinucleated histiocytes which were not typical of foreign-body giant cells. The adjoining skeletal muscle was involved by the granulomatous process.

Six lesions were found in the pulmonary specimen, varying in size up to 1.0 cm. diameter, and generally having a diameter of 0.3 cm. These were gray-white, moderately firm, indistinctly limited and apparently not associated with bronchi. There was extensive emphysema of the apical and lateral segments of the upper lobe, and four of the nodules found were in the emphysematous parenchyma.

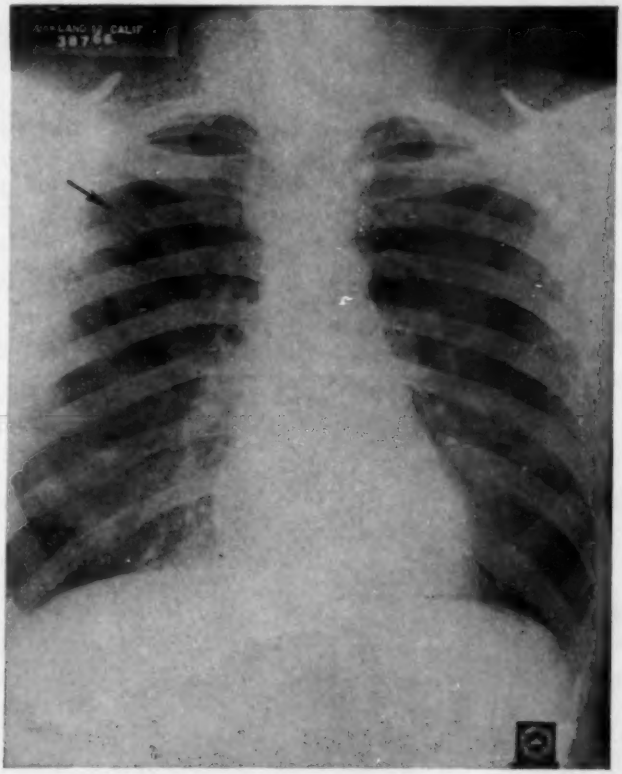

FIG. 1. *Case 1.* Chest roentgenogram showing a destructive process of the right fifth rib.

Microscopically, the pulmonary lesions were characterized by an irregular central area of dense infiltration by histiocytes and eosinophils and lesser numbers of lymphocytes and neutrophilic polymorphonuclear leukocytes. This dense collection of cells completely obliterated normal lung parenchyma (figure 2). In the largest nodule, rounded masses of histiocytes were surrounded by a ring of eosinophils (figure 3). The histiocytes had a moderate amount of foamy or pale granular cytoplasm, and their nuclei in some areas stained slightly darker and more uniformly than does the usual pale vesicular histiocyte nucleus. In one of the lesions there were a few multi-

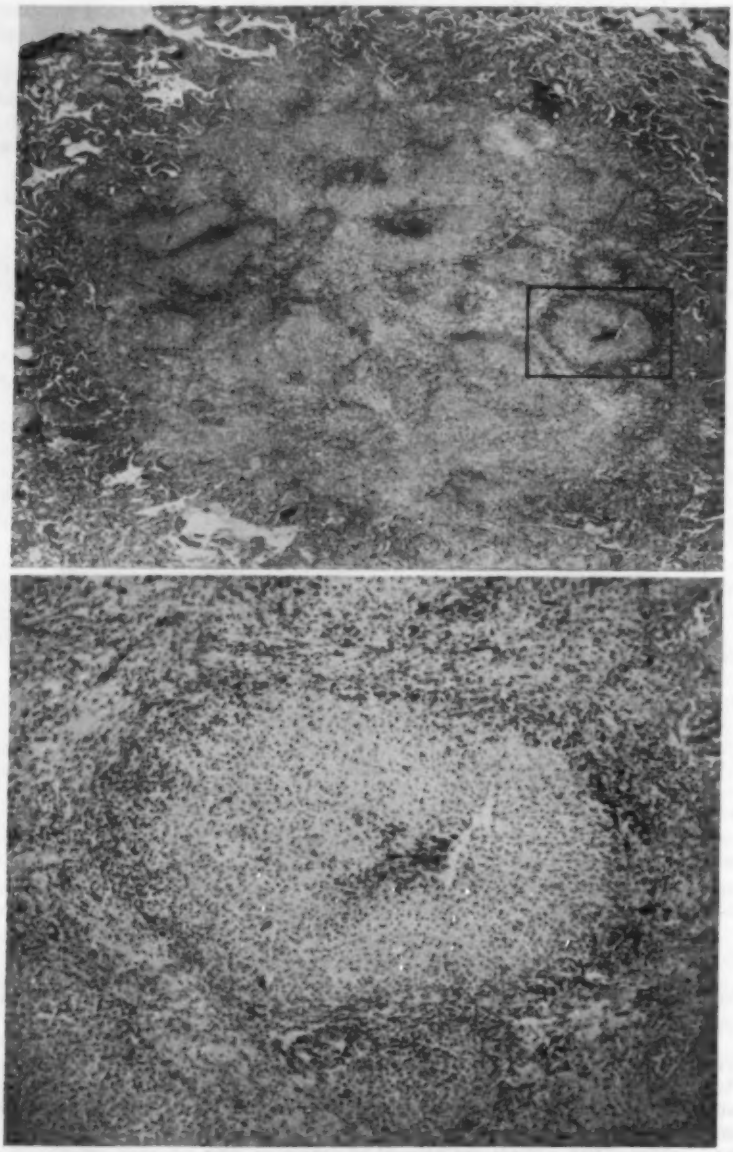

FIG. 2 (*above*). *Case 1.* Low power photomicrograph of lung lesion. Coalescence of granulomatous nodules. Hematoxylin and eosin. 32×.

FIG. 3 (*below*). *Case 1.* Higher power photomicrograph of nodule outlined in figure 2. Note dense mass of histiocytes surrounded by ring of eosinophils; central cluster of eosinophils. Hematoxylin and eosin. 90×.

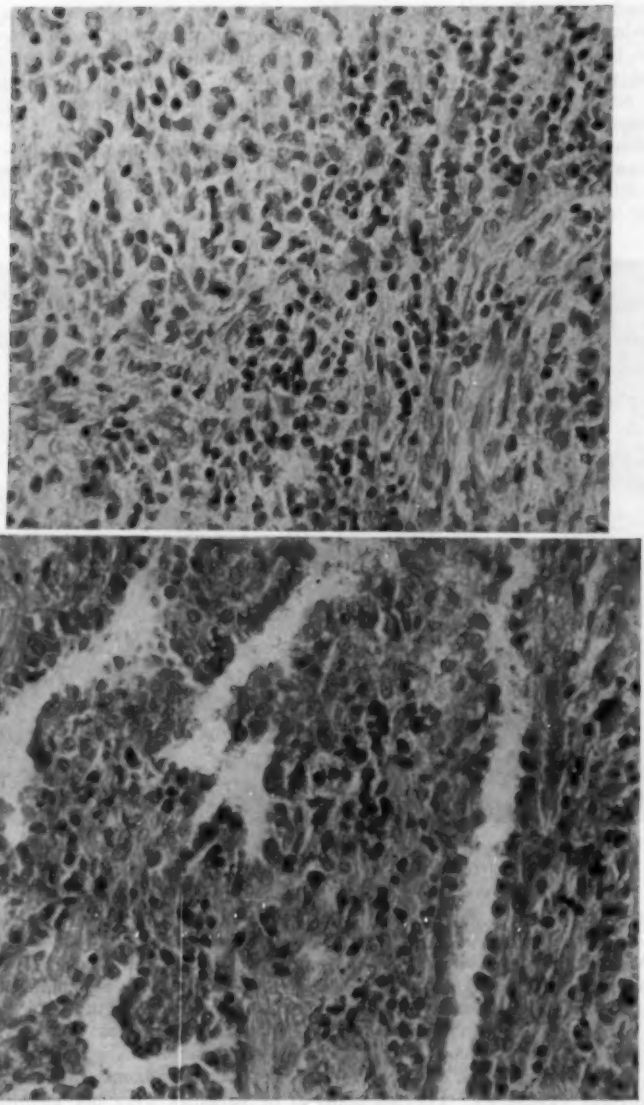

FIG. 4 (*above*). *Case 1.* Photomicrograph showing detail of lesion depicted in figure 2. Pale-staining histiocytes and darker-staining eosinophils in a scant fibrous stroma. Hematoxylin and eosin. 295 ×.

FIG. 5 (*below*). *Case 1.* Photomicrograph showing interstitial reaction at borders of lesion illustrated in figure 2. Note pleomorphic infiltration by leukocytes, and cuboidal cells lining alveolar spaces. Hematoxylin and eosin. 295 ×.

nucleated giant cells with scant cytoplasm. Scattered macrophages contained pale yellow-brown pigment or carbon pigment. The lesions generally had a sparse fibrous stroma, but some areas exhibited increasing amounts of collagenous tissue (figure 4). Special stains demonstrated marked loss of elastic fibers in the obliterated areas. There was subintimal proliferation of variable degree in arterioles and venules within the lesions, but the vascular changes were interpreted as nonspecific. The area of granulomatous inflammation was surrounded by a narrow zone of chronic interstitial pneumonitis, characterized by edema and fibrosis of the alveolar walls and moderately dense infiltration by lymphocytes, plasma cells, eosinophils, neutrophilic polymorphonuclear leukocytes and a few histiocytes. The air spaces were lined by cuboidal cells.

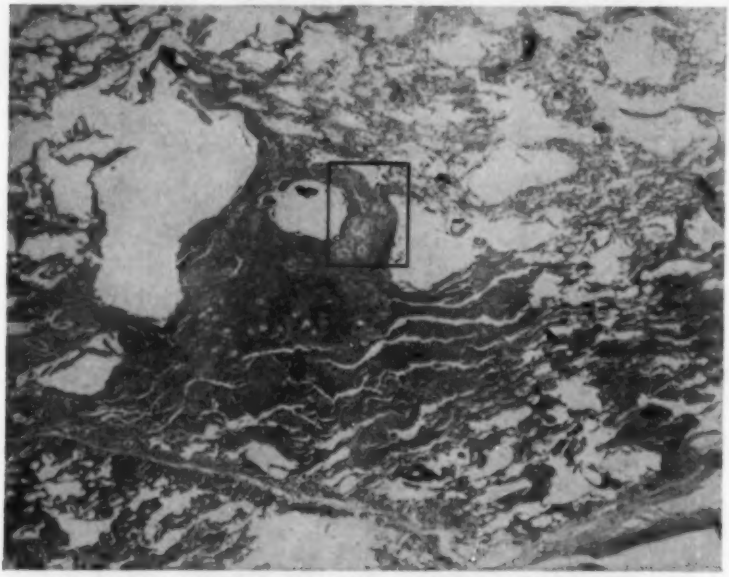

FIG. 6. *Case 1.* Photomicrograph of a 3.0 mm. lung lesion. Incomplete obliteration of normal parenchymal structure. Hematoxylin and eosin. 32×.

In these regions there was not the abundance of histiocytes and eosinophils that was observed in the central portions of the nodules (figure 5).

Also noted were small areas of moderate to intense infiltration of alveolar walls and interstitial tissue by histiocytes, eosinophils, lymphocytes and plasma cells, but with little or no obliteration of the parenchymal structure (figure 6). In some of these foci eosinophils and histiocytes were prominent, whereas in most foci these two cells were inconspicuous. The histiocytes in these lesions generally had a moderate amount of pale pink cytoplasm, while occasional xanthomatous histiocytes were also present (figure 7). Foreign material or parasites were not identified in the lesions. The pulmonary parenchyma in which these nodules were located generally was markedly emphysematous. The enlarged air spaces were traversed by well vascularized fibrous trabeculae, without the clubbed ruptured alveolar walls seen in emphysema of recent origin.

Case 2. A 28 year old housewife was admitted to the Samuel Merritt Hospital, Oakland, California, on June 26, 1952. She had been healthy until November, 1950, when she consulted her family physician because of a swelling in the left chest wall. Physical examination at that time was within normal limits with the exception of a palpable mass involving approximately three inches of the midportion of the left ninth rib. A roentgenogram of the chest showed a localized destructive enlargement of the left ninth rib, identical in position to the palpable lesion. The lung fields were interpreted as being clear (figure 8). On November 21, 1950, the rib lesion was

FIG. 7. *Case 1.* Higher power photomicrograph of area outlined in figure 6. Note xanthomatous histiocytes filling altered air spaces. Hematoxylin and eosin. 100 ×.

resected. Histologic examination of the specimen revealed an eosinophilic granuloma. Following operation she noted the gradual onset of general fatigue and increasing dyspnea. In May, 1952, she was referred to one of the authors (D. J. D.). Review of the history disclosed no additional pertinent facts. Physical examination revealed a well developed and well nourished afebrile young woman with a frequent nonproductive cough. No abnormalities were found. The surgical scar over the left ninth rib was well healed. The leukocyte count was 5,250, with a normal differential. Hemoglobin was 11.4 gm. Urinalysis was normal. Sputum smear revealed many polymorphonuclears, a few epithelial cells, a moderate number of gram-positive cocci

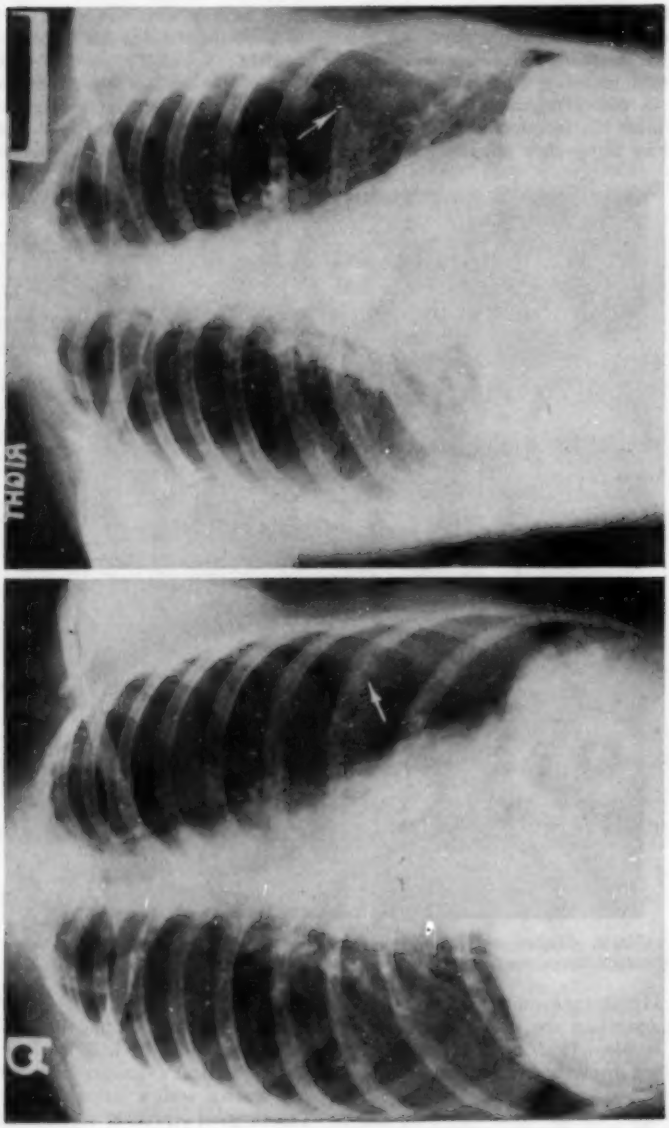

FIG. 8 (*left*). *Case 2.* Chest roentgenogram (November, 1950), showing a destructive lesion of the left ninth rib. Note slight increase of pulmonary markings.
FIG. 9 (*right*). *Case 2.* Chest roentgenogram (May, 1952), showing diffuse bilateral pulmonary infiltration.

in chains and pairs, and gram-negative cocci in pairs. The culture yielded beta hemolytic streptococci and *Neisseria catarrhalis*. Roentgenograms of the chest showed a diffuse miliary granular infiltration of both lung fields and a defect in the left ninth rib (figure 9). The roentgenograms of 1950 were reviewed and, in retrospect, interpreted as showing similar pulmonary lesions in a very early stage. Sternal bone marrow smear was not remarkable. Second strength tuberculin skin test was positive. A roentgenographic bone survey was negative. Penicillin and streptomycin therapy was ineffective. Cough, dyspnea and the roentgenographic findings remained unchanged. In the absence of a definite diagnosis a biopsy of the lung was recommended. Right thoracotomy was performed June 27. The lung was found to be diffusely granular, and a specimen excised from the lower edge of the middle lobe revealed eosinophilic granuloma microscopically. Convalescence was uneventful.

In view of the sensitivity of eosinophilic granuloma to roentgen therapy a trial dose was given to one fourth of the thoracic area. A calculated depth dose of 990 roentgens as measured at the midline of the chest was given through two external treatment ports over the right lower lobe. Subsequent roentgenograms have failed to show any appreciable change in the pulmonary lesions. The patient has felt better, although she continues to have shortness of breath and a feeling of general weakness.

Pathology: The histopathologic features of the costal lesion were similar to those described in case 1. The specimen from the lung was irregularly indurated and its cut surface presented poorly demarcated gray-white firm nodules. Microscopically the nodules consisted of irregular areas of interstitial edema and fibrosis, associated with moderately dense infiltration by histiocytes, lymphocytes and eosinophils. Lesser numbers of neutrophilic polymorphonuclear leukocytes and plasma cells were also present. In some areas the changes were more intense and thus obliterated the alveoli. Xanthomatous histiocytes predominated, and in some areas were found in large clusters (figure 10). The surrounding pulmonary tissue was irregularly emphysematous.

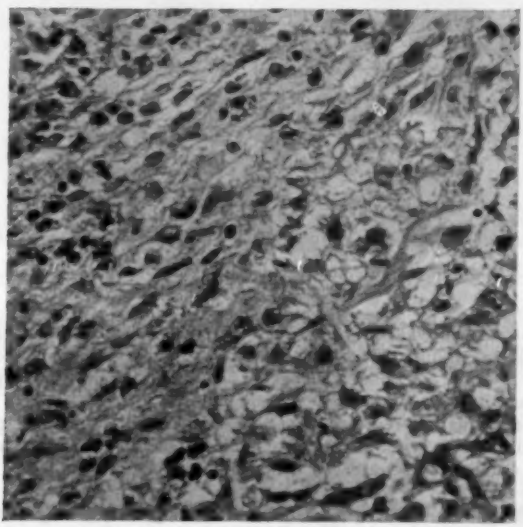

FIG. 10. *Case 2.* Photomicrograph of pulmonary lesion. Note xanthomatous histiocytes in lower right. Hematoxylin and eosin. 295 ×.

Case 3. This 36 year old housewife was admitted to Samuel Merritt Hospital, Oakland, California, on December 29, 1952, with the chief complaint of shortness of breath. In 1949 the patient had had an episode of dyspnea which was attributed to heart trouble. She was kept in bed for three months, during which time the dyspnea subsided. In June, 1952, the shortness of breath recurred and progressed. In October, 1952, a roentgenogram of the chest showed a right pneumothorax. Air was aspirated by thoracentesis on three different occasions, but the lung would not completely expand. This was attributed to a probable ruptured pulmonary cyst, and thoracotomy was advised.

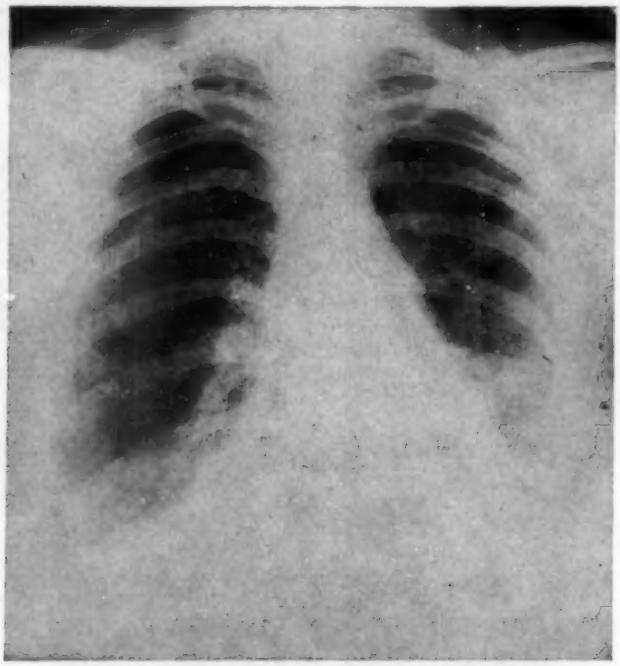

FIG. 11. *Case 3.* Chest roentgenogram showing right pneumothorax and diffuse bilateral pulmonary infiltration.

The pertinent family history revealed that the patient's father had died of tuberculosis and her grandfather of cancer. Her only serious childhood illness was manifested by pyuria, and since the age of 12 she had had severe polydipsia and polyuria day and night.

Physical examination revealed a patient who appeared in good general health. She had prominent eyes without definite exophthalmos. The trachea was in the midline. Breath sounds were decreased over the right chest throughout. Examination was otherwise normal.

The erythrocyte count was 4,820,000 and hemoglobin 16.6 gm. The leukocyte count was 9,350, with normal differential. Blood chlorides were 96.5 mEq., and potassium was 4 mEq. Roentgenograms of the chest showed a right pneumothorax

with 50 per cent collapse of the lung and a slight mediastinal shift to the left. There was diffuse symmetrical pulmonary fibrosis involving all lobes (figure 11). At fluoroscopy both leaves of the diaphragm moved adequately, but the lungs did not empty out well, indicating some obstructive emphysema. Bone survey revealed a poorly defined radiolucent zone in the neck of the left femur (figure 12).

Right thoracotomy was done on December 31, at which time pneumothorax due to a ruptured pulmonary bleb was found. The lung was diffusely granular. The bleb was sutured and the upper lobe decorticated. A small specimen taken from the inferior margin of the middle lobe was interpreted microscopically as eosinophilic granuloma. Convalescence was uneventful and the patient is now asymptomatic.

Pathology: The specimen of lung was characterized by palpable granularity and by scattered 1.0 to 2.0 mm. nodules on the cut surface. Microscopic sections of the specimen revealed focal interstitial involvement by chronic granulomatous tissue.

FIG. 12. *Case 3.* Roentgenogram of osteolytic lesion in neck of left femur.

Histiocytes and eosinophils were the dominant elements in the infiltrate, and the cytoplasm of the histiocytes was granular rather than frankly xanthoid. Obliteration of alveoli was not a feature of the lesions (figure 13). The involved pulmonary parenchyma was emphysematous.

DISCUSSION

Since its first description as a clinical entity,[1] eosinophilic granuloma has been found increasingly often in locations other than bone, and it has been considered by most authors to be related to Hand-Schüller-Christian disease. Detailed discussions of this relationship are available.[2, 4, 5, 12, 13, 14, 15] Pul-

monary infiltration in patients with proved osseous eosinophilic granuloma has been reported,[6, 7, 11] and eosinophilic granuloma of the lung was demonstrated by biopsy of the lung by Farinacci et al.[10] In their two cases bone was not involved. Three additional cases of eosinophilic granuloma of the lung are presented here. They support the concept that eosinophilic granuloma and Hand-Schüller-Christian disease are fundamentally related. In case 3 only the pulmonary lesion was biopsied. It was essentially similar

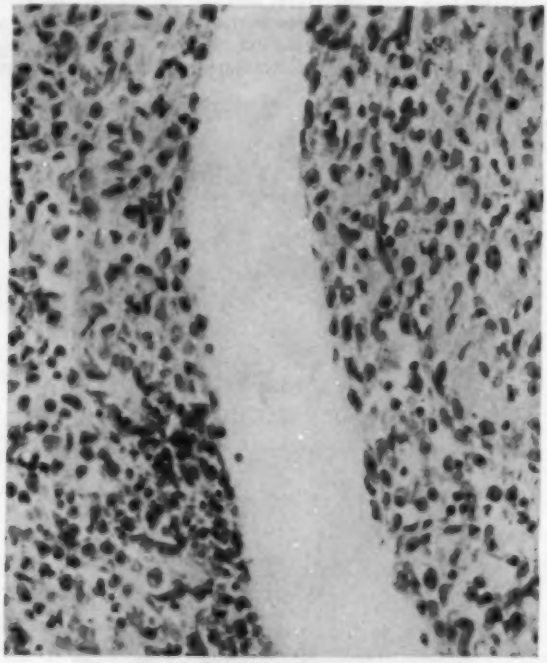

FIG. 13. *Case 3.* Photomicrograph of pulmonary lesion showing eosinophilic and histiocytic infiltration. Central clear zone represents remnant of air space. Hematoxylin and eosin. 295 ×.

to the pulmonary lesions in the first two cases. This patient also had diabetes insipidus and questionable exophthalmos. Although roentgenograms of the skull did not reveal any bony abnormality, this case is regarded as an instance of Hand-Schüller-Christian disease, a syndrome manifested by the triad of diabetes insipidus, exophthalmos and cranial defects. Cases diagnosed as having this condition do not always present all three of the classic signs. The osseous lesions involve flat bones and the proximal long bones. Pathologically the lesions are of a xanthogranulomatous nature, occasionally with collections of eosinophils. It is thought that cases 1 and

2 represent the first reported instances of histologically proved eosinophilic granuloma of both lung and bone.

Eosinophilic granuloma is regarded by the present authors as a distinct type of pathologic lesion which should not be utilized as a category in which to place a variety of unrelated lesions characterized by infiltration of eosinophilic leukocytes. As in all chronic granulomatous types of inflammation, the fundamental reactive cell is the reticuloendothelial cell, the histiocyte or macrophage. The presence of eosinophils lends distinctiveness to the lesions under discussion.

Histopathologic details of the three cases that form the basis for this report have been given above. The cellular alterations in the pulmonary lesions were similar to the pattern diagnosed as eosinophilic granuloma of bone or other structures, as well as Hand-Schüller-Christian disease. Certain distinctive features of the pulmonary infiltrations, however, deserve special comment.

In the smallest pulmonary nodules the infiltration was of an interstitial nature, and eosinophils or histiocytes were no more numerous than accompanying lymphocytes and neutrophils. The alveolar spaces remained patent. In slightly larger lesions the edematous interstitial tissue was more densely infiltrated by histiocytes and eosinophils. With further progression of the reaction there was marked thickening of the interstitial tissue, coupled with encroachment on the air spaces (figure 6). Gradually the alveoli became filled with the inflammatory cells or they collapsed completely, and an obliterative nodule was formed. Coalescence of such granulomatous foci produced a larger nodular lesion that replaced the lung parenchyma (figure 2). Along the outer margin of such obliterative lesions the interstitial reaction, as noted above, was found to persist (figure 5). An interesting feature of the coalescent nodule was the occasional outlining of dense masses of histiocytes by a ring or halo of eosinophils (figure 3).

Also of interest was the presence of emphysema in each case. Sufficient material was available in case 1 for study of this aspect, and it was concluded that the emphysema antedated the granulomatous lesions. Cunningham and Parkinson [16] reported six cases of diffuse cystic lungs of granulomatous origin, but the lesions of the present study do not resemble the findings in their cases.

Summary

Three cases of eosinophilic granuloma of the lung are reported and described pathologically. Two of these cases also had eosinophilic granuloma of bone. The third case had Hand-Schüller-Christian syndrome and a femoral bone lesion. Pulmonary lesions in all three cases were essentially identical pathologically. This appears to offer further evidence that eosinophilic granuloma of bone and Hand-Schüller-Christian disease are variants of one basic pathologic process.

Addendum

Following preparation of this report a comprehensive critical review of the subject by Dr. Louis Lichtenstein appeared in the Archives of Pathology, Vol. 56, No. 1, pages 84–102, dated July, 1953. His review is entitled: "Histiocytosis X. Integration of eosinophilic granuloma of bone, Letterer-Siwe disease, and Schüller-Christian disease as related manifestations of a single nosologic entity." An additional previously unreported case of eosinophilic granuloma involving both lungs and bone is cited therein (page 99).

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MUSCULAR RELAXATION IN TETANUS WITH SPECIAL REFERENCE TO THE EFFECT OF MEPHENESIN*

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Among the most important problems in the management of generalized tetanus are the following: the muscle rigidity, generalized muscle spasms and convulsions, causing death from severe exhaustion; respiratory failure from muscular paralysis; asphyxia from too frequent or too long maintained laryngeal spasms, and anoxemia due to obstruction of the respiratory passages. The use of d-tubocurarine chloride is fraught with danger, because almost complete curarization is required for the control of muscle spasms. Also, the effects are transitory and unpredictable, and severe respiratory depression and tracheal obstruction are at times unavoidable.[1] With the advent of 3 orthotoloxy-1, 2-propanediol (Mephenesin), favorable reports on the achievement of muscular relaxation in tetanus have already appeared in the literature.[2] We have thought it worth while to give this drug a trial.

Material and Methods

Fifteen cases were selected for the present study. There were 11 white patients (six males and five females), three Negroes (two males and one female), and one mulatto male. The youngest was 12 years old and the oldest 64, with an average of 35.2 years.

The approximate incubation period was known in 10 cases. In four, it was five days or less; in four, five to 10 days; and in two, 10 to 15 days. The average was 6.6 days. The portal of entry was discovered in 14: in the feet in five; in the leg in one; in the uterus in two; in the hand in three; in the face in two, and in the gums in one. The nature of the lesion was evident in 14: puncture wounds in four; lacerations in four; abortions in two; incised wound in one; ulcers in two, and an infected tooth socket in one.

The disease was classified as generalized tetanus in 12 and as cephalic in three. Thirteen had generalized convulsions, either on admission or afterwards. The interval between the onset of trismus and the appearance of convulsions was known in all: on the first day in seven; within two days in two; within three days in one; within four days in one; within five days in one, and within nine days in one, with an average of 2.4 days.

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Treatment was started within 12 hours to eight days after the onset of trismus: within the first day in eight; on the second day in two; on the third day in two; on the fifth in two, and on the eighth in one, with an average of 2.4 days.

On admission 14 patients received 40,000 units of tetanus antitoxin intravenously and an equal amount intramuscularly after a negative reaction to the dermal test for sensitivity to horse serum. Ten thousand units were then given intramuscularly daily for the next three consecutive days. After infiltrating the surrounding tissues with 10,000 units of tetanus antitoxin, tissue or other material, including pus when present, was obtained from all the accessible portals of entry for anaerobic cultures of the *Clostridium tetani* in thioglycollate or cooked meat media. Wide or extensive debridement was not attempted, and the wound was covered with sterile gauze. Penicillin was administered intramuscularly either as crystalline penicillin potassium (50,000 units every four hours), or as procaine penicillin G (daily intramuscular doses of 400,000 units). In the case of pulmonary bacterial complications unresponsive to penicillin, intramuscular streptomycin was given in daily 1 gm. doses. Dextrose (5 per cent) in isotonic saline solution intravenously was administered in accordance with individual needs for hydration. Phenobarbital sodium (0.13 to 0.30 gm. intramuscularly, every two to four hours) served to maintain sedation.

All the patients received a 2 per cent solution of Mephenesin intravenously in repeated doses, ranging from 25 to 300 c.c., and two received the drug in tablet form as well.

Two of the patients received tribromoethanol (Avertin) by rectum at varying intervals, and in doses of 25 to 50 mg. per kilo of body weight diluted in 100 c.c. of sterile water, after a fair trial with intravenous Mephenesin. Tracheotomy was performed in 10 cases; in nine under local 1.5 per cent procaine hydrochloride anesthesia, and in one under intravenous Sodium Pentothal. Nine patients received intravenous Mephenesin during the surgical intervention (table 1).

Results

Two patients died and 13 recovered, so that the gross mortality rate was 13.3 per cent. One of the deaths, attributed to heart disease, occurred in a hypertensive, arteriosclerotic and emphysematous 64 year old man (case 5). The fatal outcome was not attributed to the acute illness but the latter was undoubtedly contributory. Although improbable, the direct toxic effect of Mephenesin on the myocardium is also a subject for speculation in this instance.[8]

The other death, in a 17 year old boy (case 14), was directly attributed to the tetanus. Although the incubation period was not known, it was evident from the outset that the disease was extremely severe, as evidenced by the appearance of frequent violent convulsions and prolonged laryngeal

TABLE I

Case	Age	Sex	Race	Portal of Entry	Nature of Lesion	Incubation Period	Interval Between Trismus and Convulsions	Day Treatment Started	Tolserol	Avertin	Trache-otomy	Survival Days	Outcome
1	35	M	M	Nose	Laceration	4	1	1	I. V.	−	+	−	Recovery
2	28	F	W	Uterus	Abortion	7	4	1	I. V.	−	−	−	Recovery
3	19	M	W	Hand	Incised wound	2	1	1	I. V.	−	+	−	Recovery
4	50	F	W	Leg	Ulcer		5	5	I. V.	−	−	−	Recovery
5	64	M	W	Hand	Puncture wound	8	Laryngeal 2	1	I. V.	−	−	6	Death
6	17	F	W	Foot	Puncture wound	5	1	2	I. V.	+	+	−	Recovery
7	19	M	C	Foot	Laceration	6	3	1	I. V.	−	−	−	Recovery
8	38	M	W	Foot	Puncture wound	5	1	3	I. V.	−	−	−	Recovery
9	38	F	W	Uterus	Abortion	11	2	3	I. V.	−	+	−	Recovery
10	48	F	W				9	8	I. V.	−	+	−	Recovery
11	40	M	W	Forehead	Laceration	12	1	½	I. V.	−	+	−	Recovery
12	44	M	W	Gums	Tooth socket	−	2	5	I. V.	−	+	−	Recovery
13	60	F	C	Foot	Ulcer			1	I. V.	−	+	−	Recovery
14	17	M	C	Foot	Puncture wound		1	2	I. V.	−	+	5	Death
15	12	M	W	Hand	Laceration	6	1	1	I. V.	+	+	−	Recovery
Average	35.2					6.6	2.4	2.4				5.5	

spasms scarcely one day after the onset of trismus, by signs of bronchopneumonia, and by a temperature of 104° F. Tracheotomy had to be carried out, under local anesthesia with 1.5 per cent procaine hydrochloride, soon after admission. Heavy sedation with phenobarbital sodium and repeated intravenous injections of 50 c.c. of 2 per cent solution of Mephenesin, started on admission and continued, failed to control the generalized convulsions. Unfortunately, profuse bleeding supervened, and suction of the aspirated blood was not complete; death resulted from asphyxia on the fifth day of illness. At autopsy, large amounts of partially clotted blood were found obstructing the bronchi, and there was a bilateral and massive bronchopneumonia.

This experience and others have made us wonder whether tracheotomy in severe tetanus should be performed under local anesthesia, no matter how heavy the dose of sedative or how much Mephenesin is administered for muscular relaxation. It was observed in this patient that even in the presence of horizontal nystagmus, convulsions appeared during the operation, on introducing the tracheal tube, and whenever suction was attempted. In spite of its shortcomings rectal Avertin would have been the anesthesia of choice for tracheotomy in this and in others of our severe cases.

A summary of the clinical course in a case of severe cephalic tetanus is included, to illustrate the beneficial effects derived from the frequent intravenous administration of Mephenesin in recurrent laryngeal spasms, and to present one of the most common complications resulting from its use.

Case Reports

Case 1. A 35 year old mulatto laborer sustained a laceration of the bridge of the nose from a blow with a piece of wood while in a fight, December 24, 1950. During the following three days he had generalized body aches resulting from blows received in other parts of his body. On December 28 he developed severe trismus and dysphagia, as well as painful stiffness of the neck, thoracic, abdominal and leg muscles that impeded walking. On December 29 his speech became unintelligible, and he had two generalized convulsions in an interval of two hours, which prompted his admission to the San Juan City Hospital.

He had been severely constipated, and had had a low-grade fever for three days prior to admission. His past and family histories were noncontributory, aside from alcoholic addiction. He denied having received tetanus antitoxin or penicillin at any time.

The patient was an acutely ill, well developed and well nourished male, bathed in cold perspiration, with a temperature of 100° F., pulse of 120, respirations of 28 per minute, and blood pressure of 180/130 mm. of Hg. He presented a definite risus sardonicus, and was unable to open his mouth. The speech had a nasal quality and was almost unintelligible. The facial, cervical, thoracic, abdominal and leg muscles were markedly spastic and painful to the touch. The lungs and heart appeared normal, aside from rapid, mostly abdominal breathing, and tachycardia. The abdomen was generally tender to deep palpation. There was generalized accentuation of the deep tendon reflexes. An infected laceration, approximately 1.5 cm. long, was found in the upper portion of the bridge of the nose, surrounded by an extensive area of swelling and redness.

The red and white blood cell and hemoglobin values and the urine and nonprotein nitrogen were normal. The blood was strongly positive for syphilis. The feces showed many ova of *Necator americanus* and *Trichuris trichiura*.

He received 40,000 units of tetanus antitoxin intravenously, and 40,000 units intramuscularly on admission, after a negative dermal test for sensitivity. A small biopsy was taken of the portal of entry for culture of the *Cl. tetani*, after infiltration of the surrounding tissue with 10,000 units of tetanus antiserum. The culture was positive within 24 hours. Debridement was not attempted, and the wound was left covered with dry sterile gauze. He was given daily doses of 10,000 units of tetanus antitoxin intramuscularly for three consecutive days. Procaine penicillin G (Squibb), in daily doses of 400,000 units, was given intramuscularly for four days, followed by 600,000 units daily. Streptomycin (1 gm. doses daily) was started on the third day. Phenobarbital sodium (.20 gm.) was given intramuscularly every four hours for sedation. Mephenesin, 50 c.c. of a 2 per cent solution, was administered intravenously every four hours, and 1,000 c.c. of 5 per cent dextrose in isotonic solution were given intravenously every 12 hours to maintain hydration.

Almost perfect muscular relaxation was maintained for 10 hours after the initial administration of Mephenesin. However, at 5:30 a.m. on December 30 he had a violent generalized convulsion which lasted five minutes, accompanied by severe laryngeal spasm for two minutes. This was followed by another generalized convulsion which lasted 15 minutes. At that time the blood pressure was 210/110 mm. of Hg. and the pulse was regular at 120 per minute. Phenobarbital sodium intramuscularly (0.30 gm.) and 50 c.c. of 2 per cent of Mephenesin intravenously controlled the convulsions. Oxygen was started by nasal catheter at a rate of 6 L. per minute. The patient spent a fairly good day; the lungs were clear to percussion and auscultation, and the blood pressure dropped to 150/110 mm. of Hg.

At 11 a.m. on December 31 the patient developed deep cyanosis secondary to repeated and prolonged laryngeal spasms, and tracheotomy was performed under local anesthesia with 1.5 per cent solution of procaine hydrochloride, deep sedation, and 100 c.c. of 2 per cent solution of Mephenesin, given slowly by vein. Good muscular relaxation was attained. Large amounts of secretion were aspirated through the tracheotomy tube, and oxygen was administered by the same route.

On January 1, 1951, the patient developed high fever (103° F.), and numerous râles were heard over both pulmonary bases, but he appeared better and his breathing had improved. At this time the leukocyte count was 10,500, with 82 per cent neutrophils. He could answer questions and, although the abdominal muscles were still spastic, could open his mouth for approximately 2 cm. However, it was noted that his left arm was swollen and tender, suggesting acute thrombophlebitis. Mephenesin was discontinued.

On January 5 the temperature began to decline, and the lungs were clear to percussion and auscultation. Phenobarbital sodium was continued in doses of 0.13 gm. every six hours, and the streptomycin was discontinued. The temperature had reached normal levels by January 8. At this time the patient was able to open his mouth 3 cm., and he felt hungry.

He was out of bed by January 18, but in spite of a marked reduction in the generalized muscle spasms he was still unable to stand without help. On January 20 he was able to move his arms and legs freely, and to stand unaided, but moderate trismus remained. It was not until January 25 that he was able to walk. The tracheal tube was removed on February 2, and he was discharged from the hospital on February 10. When he was seen on April 25 the blood pressure was 160/110 mm. of Hg, but he was otherwise in good health.

Comment: This is illustrative of very severe cephalic tetanus in a hypertensive patient, with a short incubation period and a very short interval

between the onset of trismus and the appearance of convulsions. He was twice on the verge of death from asphyxia as the result of frequent and prolonged laryngeal spasms. The first episode was relieved by the administration of Mephenesin, while during the second tracheotomy it was life-saving.

It is evident that Mephenesin was a useful adjuvant in the management of this patient. Not only did it help in controlling the convulsions before tracheotomy, but it also served a useful purpose during the operation, when muscular relaxation was greatly needed. However, the short duration of its beneficial effects and the probable rôle in the production of thrombophlebitis at the site of injection emphasize the time limitations and dangers of its use.

Case 2. A 28 year old white Puerto Rican housewife, who previously had had two provoked abortions, was criminally submitted to the introduction of an "iron rod" into the uterus, followed by a rubber catheter, at 7 p.m. on March 17, 1950. At 12 a.m. on the same day she started to bleed per vaginam, and she noted the passage of a fetus at 7 a.m., March 18. On March 24 (seven days later), at about 3 p.m., she began to notice rigidity of the muscles of the face, neck and back. Around midnight of the same day severe trismus and dysphagia appeared, forcing her admission to the San Juan City Hospital next day. The past and family histories were negative, aside from amenorrhea for two months before the abortion. She had not received tetanus antiserum prior to or after the onset of the illness, but she claimed to have had an intramuscular injection of an unknown quantity of penicillin after the abortion.

The patient was a well developed, fairly well nourished 28 year old white female in acute distress, with a temperature of 99.6° F., pulse of 90, respirations of 24 per minute, and blood pressure of 110/90 mm. of Hg. She presented marked nuchal rigidity, moderate opisthotonos, spastic facial muscles with severe trismus, moderate spasticity of the abdominal and leg muscles, and deep tendon hyperreflexia. Vaginal exploration revealed a parous introitus, an anterior cervical erosion, a marked inflammation around the external os, and abundant purulent discharge draining from the endocervical canal. The uterus was moderately enlarged and retroflexed. The uterus must have been the portal of entry.

The blood values, catheterized urine and blood tests for syphilis were normal. The stools were positive for ova of *T. trichiura*. Anaerobic cultures of the uterine discharge failed to produce the *Cl. tetani*.

She received 40,000 units of tetanus antiserum by vein and 40,000 units intramuscularly after a negative dermal test for sensitivity. Ten thousand units were given intramuscularly daily for three consecutive days after admission. Sodium phenobarbital (0.13 to 0.20 gm.) was administered intramuscularly every four hours for sedation, and 400,000 units of procaine penicillin G (Squibb) were given intramuscularly every 24 hours. This was omitted on her sixth hospital day, after the appearance of a rash attributed to the antibiotic. She received 1,000 c.c. of 5 per cent glucose in physiologic saline solution intravenously every 12 hours for hydration.

She did fairly well, aside from marked trismus and generalized spasticity of the skeletal musculature, until March 28 (11 days after the abortion and four days after onset of trismus), when she developed generalized convulsions when lightly stimulated. The temperature rose to 102° F.

At 4 p.m. on March 29 she began to bleed per vaginam, and the convulsions became worse. On March 30, at 4:45 p.m., Mephenesin (50 c.c. of a 2 per cent solution) was slowly administered intravenously. The patient developed a horizontal nystagmus, and the generalized muscle spasms were relieved. Aside from moderate nuchal rigidity, there was almost complete muscular relaxation. By 5:20 p.m. the

effect of the drug was wearing off, but she was still able to open the mouth for 3 cm. The horizontal nystagmus persisted until 6:05 p.m., at which time severe trismus and generalized muscular rigidity reappeared. The muscular relaxation persisted for approximately 80 minutes after the injection of Mephenesin. An additional 25 c.c. of the drug was given after an interval of five minutes. The horizontal nystagmus reappeared after the injection of 20 c.c. Immediately afterwards, 75 c.c. were given in 500 c.c. of 5 per cent glucose in water, at a rate of 60 drops per minute. Partial relaxation was attained after the slow injection of the 2 per cent solution of the drug, and this persisted for 70 minutes, but the spastic state returned before the intravenous infusion was completed.

At 9:45 a.m. on March 31, 50 c.c. of the undiluted relaxant solution were given intravenously in 10 minutes. Within five minutes (25 c.c.), horizontal nystagmus and marked muscle relaxation, excluding the muscles of the neck, were observed. The relaxed state persisted for 75 minutes. On the return of the spastic state at 11 a.m., she received 50 c.c. of the drug, with complete muscle relaxation for 90 minutes. At this time the nystagmus was very marked, and she complained of severe pain at the site of the injection. Convulsions reappeared at 12:30 p.m., and another 50 c.c. of Mephenesin solution were administered at 1 p.m., with striking results. The musculature became flaccid, she could open the mouth widely, and both horizontal and vertical nystagmus was observed for approximately 90 minutes. It was decided to continue the administration of the drug in doses of 50 c.c. every three hours, using the unaffected arm for the intravenous injections. It was observed that good muscle relaxation was attained, but light stimuli and loud noises would lead to muscle spasms within an average of 90 minutes after each injection, and permanent relaxation could not be attained when the drug was administered by this method. The drug was discontinued because of bilateral thrombophlebitis of the arms, but by this time the patient could open her mouth 3 cm. After the penicillin had been discontinued on April 1, because of generalized urticaria, she was started on 500 mg. of Aureomycin (Lederle) by mouth every six hours. The generalized convulsions persisted until April 4. On April 5 the spasticity of the muscles partially receded, she could open the mouth to approximately 4 cm., and she began to ingest soft food. The dose of phenobarbital sodium was reduced to 0.13 gm. every six hours, and she could sit up in bed. All medication was discontinued on April 15. On April 24 she was able to walk. The condition of the arm veins improved rapidly with passive exercise and local medication, and she was discharged on April 26. When seen on May 25 she was found to be in good health, aside from slight weakness and occasional headache. The neurologic examination was essentially normal.

For the sake of clarity, the effect of Mephenesin on this patient will be summarized in tabular form.

Date	Hour	Dose	Method	Interval of Relaxation in minutes	Results
March 30	4:45 p.m.	50 c.c. of 2% Sol.	Undiluted	80	Good
	6:05 p.m.	25 c.c. of 2% Sol.	Undiluted		Good
	6:10 p.m.	75 c.c. of 2% Sol.	500 c.c. of 5% glucose in H_2O	75	Poor
March 31	9:45 p.m.	50 c.c. of 2% Sol.	Undiluted	75	Good
	11:00 p.m.	50 c.c. of 2% Sol.	Undiluted	90	Good
	1:00 p.m.	50 c.c. of 2% Sol.	Undiluted	90	Excellent
	3:30 p.m.	50 c.c. of 2% Sol.	Undiluted	90	Excellent
	6:30 p.m.	50 c.c. of 2% Sol.	Undiluted	90	Excellent
	9:30 p.m.	50 c.c. of 2% Sol.	Undiluted	90	Excellent
April 1	12:30 a.m.	50 c.c. of 2% Sol.	Undiluted	90	Excellent

Comment: This is a case of severe postabortal tetanus, with an incubation period of seven days and an interval between the appearance of trismus and the onset of convulsions of four days. The severe generalized convulsions were transitorily controlled by Mephenesin. The drug had to be discontinued because of thrombophlebitis of the arm veins, but by this time the patient was improved, and the convulsions disappeared three days later.

The favorable and unfavorable properties of Mephenesin as a muscular relaxant are well illustrated. It relieved the laryngeal spasms and maintained relaxation for 70 to 90 minutes after each intravenous injection of 50 c.c. of the 2 per cent solution. However, its use has time limitations even when given to the point of toxicity, and the danger of thrombophlebitis is evident. It is clear that this patient would have required 50 c.c. of the undiluted solution intravenously every 90 minutes to maintain continuous relaxation.

It appears that this patient was not in serious danger of death from respiratory paralysis, or from asphyxia due to prolonged laryngeal spasms. With the other measures, Mephenesin was a useful adjuvant, perhaps obviating tracheotomy.

A case of severe generalized tetanus with pulmonary complications is next presented, with detailed observations on the effect of different rates of intravenous infusion when the drug is diluted in 5 per cent dextrose in water, and to emphasize the variations in tolerance.

Case 3. A 19 year old white male suffered an accidental knife wound of the third and fourth fingers of the right hand on April 21, 1950, and did not seek medical attention. On April 23 he noticed stiffness of the neck, back and facial and abdominal muscles, and some dysphagia. On April 24 severe trismus appeared, together with marked dysphagia, and frequent spasms of the muscles of the back, neck, leg and abdomen, which forced his admission to the San Juan City Hospital on that date. He denied having received antibiotics or tetanus antiserum.

He was a well developed and well nourished youth in moderate opisthotonos, bathed in profuse perspiration, with a temperature of 100° F., pulse of 100, and respirations of 30 per minute, and a blood pressure of 120/80 mm. of Hg. There was marked spasticity of the facial, neck, back, abdominal and leg muscles. A shallow incised wound, 2 cm. long and surrounded by a wide erythematous and swollen area, was encountered in the anterior surface of the third and fourth fingers of the right hand.

The red cell and hemoglobin values were normal; the white cell count was 18,300, with 85 per cent neutrophils. The urine and spinal fluid were normal. The stools showed ova of *Ascaris lumbricoides*. Anaerobic cultures for the *Cl. tetani* were repeatedly negative.

Because of a positive dermal test for sensitivity to horse serum, the patient was given 220,000 units of diluted tetanus antitoxin in divided doses during the first 36 hours. During this interval he had several generalized convulsions, severe oppression of the chest and profuse sweating. He was given phenobarbital sodium (0.19 gm. intramuscularly every three hours), 3,000 c.c. of 5 per cent glucose in saline solution intravenously every 24 hours, and daily injections of 400,000 units of procaine penicillin G (Squibb). The portal of entry was left untreated.

On April 25 his condition was critical. The temperature was elevated to 104° F. There were dullness to percussion and subcrepitant râles over the base of the right

lung, and he was having frequent convulsions. At this time Mephenesin was started, with the following results:

April 25, 3:00 p.m.: Marked generalized spasticity. Severe generalized and painful muscle spasms and generalized convulsions are frequent. Mephenesin (300 c.c. of 2 per cent solution) in 500 c.c. of 5 per cent glucose in water was started at a rate of 30 drops per minute.

3:05 p.m.: The patient still reacts to touch and loud noises with violent convulsions.

3:15 p.m.: Only mild improvement in the muscle spasms, but patient is asleep. When touched, or after loud noises, he has generalized convulsions and "howls" loudly.

3:17 p.m.: Went back to sleep, and is moderately relaxed.

3:25 p.m.: Had bouts of generalized muscular contractions every 15 seconds without provocation.

3:35 p.m.: The gastrocnemius muscles are more relaxed than the quadriceps. The abdominal and cervical muscles are almost completely relaxed. The patient is sleeping soundly. The pupils are contracted.

3:40 p.m.: The patient had another convulsion during examination. It is difficult to evaluate the presence of nystagmus because he had a convulsion every time the examiner opened his eyes. The rate of the infusion was increased to 55 drops per minute.

4:25 p.m.: Relaxation is unchanged. The rate of infusion was increased to 75 drops per minute.

4:45 p.m.: The patient is less irritable to touch. Had convulsions when stimulated.

4:55 p.m.: The patient slept for 10 minutes, but was awakened when touched.

5:05 p.m.: Convulsions at intervals, and whenever he is stimulated. No nystagmus observed.

6:30 p.m.: Convulsions occur when touched, or when awakened by a loud noise. Very irritable. Rate of infusion increased to approximately 125 drops per minute.

6:35 p.m.: Patient is asleep. Fair muscular relaxation. Patient voided in bed.

6:40 p.m.: Good muscular relaxation. Sleep unaffected by direct stimulus or noise.

7:10 p.m.: Awakened when examined. No nystagmus. Almost complete muscular relaxation.

Thus, with 300 mg. of Mephenesin, partial to complete relaxation was attained for approximately four hours. Convulsions occurred whenever the patient was stimulated or awakened by a loud noise when the rate of administration was no more than 30 to 75 drops per minute. With an increase to 125 drops per minute full muscular relaxation was evident. Muscular rigidity and convulsions reappeared a few minutes after the completion of the intravenous infusion.

On April 26, although the convulsions were less frequent, the pneumonic process in the right lung was more extensive. Tracheotomy was performed under local anesthesia and intravenous Mephenesin. Oxygen was given by tracheal catheter at a rate of 6 L. per minute. Aureomycin (0.5 gm. intravenously every six hours for two days) failed to alter the pulmonary picture. On May 3 the patient was started on 1 gm. of streptomycin daily. On May 4 the abdominal muscles were moderately relaxed, the trismus was decreased, and, in spite of a spike of fever to 104° F. on May 5, the improvement in muscular relaxation persisted. Sodium phenobarbital (0.13 gm.) was continued every eight hours. On May 9 the temperature started to recede, reaching normal on May 14. On May 10 he began to take food by mouth, and the lungs seemed normal. Complete relaxation was not attained until May 28, when he began to walk without assistance. He was discharged on June 2.

A case of moderately severe tetanus in a 50 year old woman serves to illustrate the beneficial effects of Mephenesin in selected cases.

Case 4. A 50 year old white housewife was in good health, aside from an ulcer in the medial aspect of the left ankle of eight months' duration, when on March 3, 1949, she developed marked stiffness of the jaw and dysphagia. The trismus and dysphagia became intensified, and extremely painful muscular rigidity of the neck, back, abdominal and leg muscles appeared on March 5. On March 7 she had several generalized convulsions, occurring hourly and lasting for approximately two minutes; these prompted her immediate admission to the San Juan City Hospital. She denied having received antibiotics or tetanus antitoxin.

She was a well developed and well nourished, acutely ill 50 year old white woman in marked distress, with generalized painful muscle spasms, moderate opisthotonos, extreme trismus and frequent generalized convulsions of short duration. The temperature was 101° F., the pulse 104, the respirations 26 per minute, and the blood pressure 170/110 mm. of Hg. The lungs were clear to percussion and auscultation. The heart was moderately enlarged to the left and downwards, but there were no other abnormal cardiac signs. All deep reflexes were hyperactive. The abdominal muscles were markedly spastic. There was a round, shallow, infected ulcer in the inner aspect of the left ankle, measuring approximately 4 cm. in diameter and draining a moderate amount of yellow pus.

Red cell and hemoglobin values were within normal. The white cell count was 11,000, with 77 per cent neutrophils, 18 per cent lymphocytes and 5 per cent eosinophils. The blood tests for syphilis were negative. The urine and stools were normal. Anaerobic cultures of material obtained from the portal of entry were positive for *Cl. tetani* on March 9 and negative on March 10.

She received 40,000 units of tetanus antitoxin intravenously and 40,000 units intramuscularly, after a negative dermal test for sensitivity. Ten thousand units were also given intramuscularly daily for three consecutive days after admission. Debridement was not attempted, but the area around the portal of entry was infiltrated with 10,000 units of tetanus antiserum prior to taking material from this site for culture of the *Cl. tetani*. Phenobarbital sodium (0.13 gm.) was administered intramuscularly every three hours, and 1,000 c.c. of 5 per cent glucose in normal saline solution were given intravenously each day for hydration. Crystalline penicillin potassium (Squibb) (50,000 units intramuscularly every four hours) was started on March 9, and was continued in conjunction with 1 gm. of streptomycin intramuscularly daily after March 14.

On March 10 the patient had convulsions approximately every half-hour and whenever stimulated. She was given 50 c.c. of 2 per cent solution of Mephenesin intravenously very slowly, and the following observations were made:

	Before injection	*After injection*
Ability to open mouth	2 cm.	5 cm.
Ability to move mouth sideways	Unable	Able
Abdominal rigidity	Marked	Slight
Rigidity of arms on passive motion	Marked	Slight
Opisthotonos	Marked	None
Ability to sit up in bed	Unable	Able (with help)
Dysphagia	Marked	Drank 300 c.c. of eggnog
Knee and ankle jerks	4+	++
Biceps and triceps reflexes	4+	++
Convulsions	Present	Absent
Speech	Unintelligible	Intelligible

Lasting effects: 75 minutes

Since convulsions continued at very short intervals on March 11, it was decided to administer repeated intravenous injections of 100 c.c. of 2 per cent Mephenesin diluted in 500 c.c. of 5 per cent dextrose in water, at a rate of 80 drops per minute. Muscular relaxation was attained for approximately 3.5 hours. The treatment was continued during March 12 and 13, with identical results, affording the patient a peaceful sleep that was not interrupted by either direct stimulation or loud noises, but it was observed that a radical diminution in sedation led to marked irritability, accompanied by restlessness, without convulsions.

The cessation of therapy with Mephenesin led to a rapid return of the spastic state until March 16, when the temperature and blood pressure returned to normal and the general symptoms improved. The antibiotics were discontinued on March 23, and the sodium phenobarbital and intravenous fluids on April 2, when she was able to swallow. By April 14 she was able to walk, and on April 20 she was discharged. When seen on May 18 the ulcer of the right leg was completely healed, and she presented no symptoms related to her previous illness.

Comment: This is a moderately severe case of generalized tetanus in a 50 year old woman, illustrating the beneficial effects of repeated doses of Mephenesin administered intravenously, diluted in 5 per cent dextrose in water. No complications were observed, in spite of repeated injections, during a prolonged period of observation. Emphasis is given to the fact that while the injection of 50 c.c. of the 2 per cent solution of the drug led to almost perfect muscular relaxation for 75 minutes, 100 c.c. of the diluted drug prolonged the beneficial effects to approximately 3.5 hours. Since no deleterious effects were observed, it appears that this would be the method of choice for the administration of Mephenesin in selected cases, when large and frequent doses of it are required. It must be reëmphasized that, although she was not at any time in danger of death from asphyxia, and in spite of her uneventful recovery without complications, tracheotomy was indicated from the outset because of her age and cardiovascular status. Attention is also called to the variable tolerance to the drug.

The case next summarized is one of mild tetanus in an elderly man with emphysema, hypertension and arteriosclerotic heart disease, who was benefited by Mephenesin and who died from a cardiac accident when on the way to recovery from the acute illness.

Case 5. A 64 year old white Puerto Rican laborer sustained a puncture wound in the dorsum of the right middle finger with a rusty wire on December 31, 1950. Within the next 24 hours marked swelling and severe pain in the finger supervened and he was given local treatment with hot water compresses, which led to some improvement. On January 8, 1951, he was taken with fever, headache, moderate trismus, and painful stiffness of the neck, back and abdominal muscles. The patient had had marked dyspnea on exertion and two-pillow orthopnea for six months prior to admission. He denied previous medication with tetanus antitoxin or penicillin.

He was an acutely ill, well developed and well nourished 64 year old white male with definite risus sardonicus and moderate opisthotonos. The temperature on admission was 99° F., the pulse 96, the respirations 30 per minute, and the blood pressure 160/110 mm. of Hg. There was marked spasticity of the muscles of the neck, face, back, abdomen, arms and legs, and he complained bitterly of oppression of the chest while being examined. There were noted a bilateral arcus senilis, opacity of both lenses and moderate anisocoria. He could not open his mouth more than 1 cm.

The lungs showed advanced senile emphysema, and moist râles were heard over both lung fields, especially over the left lung base. The heart could not be outlined by percussion because of the marked emphysema. The cardiac sounds were distant and of poor quality, and no murmurs were audible. The abdominal musculature was markedly spastic. The dorsum of the right hand was swollen, reddened and tender. On the dorsum of the proximal portion of the right middle finger there was a secondarily infected small puncture wound with a slight excavation draining a small amount of pus. The peripheral vessels were hardened and tortuous. The deep tendon reflexes were exaggerated.

The red cell and hemoglobin values were normal. The total white blood cells were 10,350 per cubic millimeter, with a differential of 79 per cent neutrophils, 19 lymphocytes and 2 eosinophils. The blood test was negative for syphilis. The urine was normal except for a low specific gravity of 1.005 in the morning sample.

The patient received 40,000 units of tetanus antitoxin intravenously and 40,000 units intramuscularly, after a negative dermal test for sensitivity to horse serum. The neighborhood of the portal of entry was infiltrated with 10,000 units of tetanus antiserum, and necrotic tissue and pus were obtained for anaerobic cultures, which gave positive results for *Cl. tetani* on the sample taken on admission, and negative 24 hours after the initiation of therapy with daily intramuscular injections of 300,000 units of procaine penicillin G for 3 days, and 600,000 units afterwards. For three consecutive days after admission he was given daily doses of 10,000 units of tetanus antitoxin. Phenobarbital sodium (0.13 gm.) was administered intramuscularly every four hours, and 2,000 c.c. of 5 per cent glucose in water were given intravenously daily.

At 8 a.m. on January 10 the blood pressure was 150/100 mm. of Hg, the pulse 110, the respirations 30 per minute, and the temperature 101° F. He had painful generalized muscle spasms when stimulated but no frank convulsions. There was dullness over the right pulmonary base, with numerous subcrepitant râles. At 1 p.m. the blood pressure was 140/110 mm. of Hg. He was coughing but unable to expectorate, and his abdominal muscles were very tense. At 1:30 p.m. he developed stertorous breathing at a rate of 46 per minute, and became deeply cyanotic when laryngeal spasms appeared. After an injection of 50 c.c. of 2 per cent Mephenesin solution the laryngeal spasms disappeared and there was almost complete muscular relaxation for an hour. Oxygen was administered by nasal catheter at a rate of 7 L. per minute.

On January 11 the blood pressure was 140/110 mm. of Hg, the pulse 96, the respirations 32, and the temperature 100° F. The generalized muscular rigidity with opisthotonos was evident. Abundant bronchial secretions were inadequately aspirated through a rubber catheter. Both lungs presented coarse râles and rhonchi, and the right pulmonary base remained dull to percussion, with numerous subcrepitant and crepitant râles. On January 12 the temperature rose to 104° F., but the picture was otherwise unchanged, and the patient was started on 1 gm. of streptomycin intramuscularly daily.

At 11 p.m. on January 13 the blood pressure was 152/104 mm. of Hg, the pulse rate 88, the respirations 28, and the temperature had dropped to 102° F. It was noted that the pulmonary picture had improved, but dullness to percussion and scattered râles were still audible over the right base. The trismus, opisthotonos and abdominal muscular rigidity were unchanged, but there were no convulsions. The swelling of the hand had subsided, and the portal of entry was almost completely healed.

At 8 a.m. on January 14 the secretions from the upper respiratory passages were easily removed by suction, and the patient was breathing comfortably. He had a clear sensorium, the muscular rigidity was markedly diminished, and he felt very much improved. At 2 p.m. on the same day, a few minutes after having talked to his relatives during the usual hospital visit, he suddenly ceased to breathe. The immediate

examination of the cadaver by one of the medical residents on duty failed to reveal the presence of cyanosis. The autopsy was denied by his relatives.

Comment: This is a case of mild tetanus exemplifying the unfavorable prognosis of the disease in aged patients with severe emphysema, hypertension, degenerative heart disease, and an additional bacterial pulmonary complication (pneumonia). It appears as though death had resulted from a major cardiac accident, rather than from tetanus or aspiration pneumonia. Mephenesin was life-saving in asphyxia resulting from laryngeal spasms. Although tetanus was probably not the cause of death in this instance, the inescapable truth is that more heroic and timely measures might have been life-saving. Tracheotomy should have been performed at the first sign of laryngeal spasm. Removal of the bronchial secretions through the tracheotomy tube might have prevented the aspiration pneumonia. Oxygen therapy would have been more efficacious, and the increased load on the circulation, imposed by the discomfort of aspiration through a rubber catheter, would have been diminished. The fact is reëmphasized that the outcome in tetanus is dependent upon numerous factors, of main importance being the age and the state of health of the patient. The presence or absence of convulsions is a very undependable gauge in evaluating the severity of the disease.

A summary of a case of severe tetanus in a girl illustrates a failure with intravenous and orally administered Mephenesin, another complication (anesthesia of the buccal and pharyngeal mucosa when given by mouth), the beneficial effects derived from Avertin as a muscle relaxant, and the need of proper debridement of the portal of entry in specific instances.

Case 6. A 17 year old white female sustained a puncture wound in the left big toe with a splinter of wood on August 10, 1951. On August 15 she developed marked trismus and dysphagia, and on August 17 was admitted to the San Juan City Hospital after the appearance of oppressive chest pain and marked rigidity of the neck, back, abdominal, leg and arm muscles which rendered her unable to walk. There was no fever, generalized weakness or headache 12 hours prior to admission. Her past and family history were noncontributory. She had not received penicillin or tetanus antiserum prior to the present illness.

She was a well developed and fairly well nourished, acutely ill white girl in mild opisthotonos, with a temperature of 100° F., a pulse of 100, respirations of 28 per minute, and a blood pressure of 120/70 mm. of Hg. She was unable to open her mouth more than 1 cm., and the neck, back, abdominal, leg and arm muscles were spastic. There was generalized hyperactivity of the deep tendon reflexes. There was a small puncture wound in the left big toe, surrounded by a wide area of redness and swelling.

The blood values showed a mild secondary anemia but were otherwise normal, aside from moderate leukocytosis. The urine was normal. The blood serum was negative for syphilis. The stools were negative for ova or parasites.

She received 40,000 units of tetanus antitoxin intravenously and 40,000 units intramuscularly after a negative dermal test for sensitivity to horse serum, and 10,000 units were injected intramuscularly daily for the next three days. The neighborhood of the portal of entry was infiltrated with 10,000 units of tetanus antiserum, and pus and necrotic tissue were obtained for anaerobic culture of *Cl. tetani*, prior to the intramuscular administration of 50,000 units of crystalline penicillin potassium (Squibb)

every four hours. Phenobarbital sodium (0.13 gm.) was given intramuscularly every four hours, and 1,000 c.c. of 5 per cent glucose in physiologic saline solution were given intravenously every 12 hours.

The patient had generalized muscle spasms, and appeared extremely toxic during her first day in the hospital. For the prevention of frank convulsions or serious prolonged laryngeal spasms she was given Mephenesin in doses of 50 c.c. of a 2 per cent solution intravenously at 2 p.m. and at 8 p.m., and she was started on 1 gm. of Mephenesin orally (tablets crushed and mixed with water) every four hours. She derived temporary muscular relaxation from the intravenous Mephenesin but not from the orally administered doses. On August 18 the patient stated that her mouth and throat were "anesthetized" and the oral Mephenesin was stopped. Because of frequent muscle spasms and the appearance of laryngeal spasms, she was submitted to a tracheotomy at 9:15 a.m. on August 18. This was done under local anesthesia (1.5 per cent procaine) and during the intravenous administration of 50 c.c. of a 2 per cent solution of Mephenesin. Transitory laryngeal spasms and mild convulsions were observed on inserting the tracheotomy tube and when the bronchial secretions were aspirated. Fifty additional cubic centimeters were required after the completion of the operation to prevent severe convulsions.

On August 19 the temperature rose to 103° F. The muscle spasms continued frequently. Streptomycin was started daily in 1 gm. doses. Mephenesin yielded only a transitory relief for no more than 75 minutes after each intravenous injection of 50 c.c. of 2 per cent solution.

On August 20 her condition was desperate. Avertin, in doses of 50 mg. per kilo, diluted in 100 c.c. of distilled water, was started per rectum at 8:50 p.m. Relaxation was attained until midnight, when another retention enema was given. It was not until 1 p.m. on August 21 that generalized muscle spasms and restlessness reappeared. An equal amount of Avertin relieved the condition until 11:15 a.m. next day. Almost complete and continuous muscle relaxation could be attained when the drug was administered every six to 12 hours. On August 23 the temperature was 99.3° F., and she had three generalized convulsions while having the retention enema. A reduction in the dose of Avertin to 25 mg. per kilo led to a shorter interval of muscular relaxation, but by this time the patient was considered to be on her way to recovery, and the drug was discontinued on August 27, at which time the temperature was normal and she was asking for food.

In spite of the general improvement the generalized spasticity of the musculature persisted, and the patient was again started on 1 gm. of Mephenesin orally every four hours, but it failed to produce relief in 12 days. On September 10 it was observed that the portal of entry had failed to heal, and that the neighboring area was still swollen. Anaerobic cultures for *Cl. tetani* were reported as positive on August 17, 18, 19 and 20. Wide debridement of the portal of entry revealed the presence of some pus, and of a splinter of wood that, when cultured anaerobically, yielded *Cl. tetani* on September 12. A culture repeated on September 13 was negative. The tracheotomy tube was removed on September 14. The muscular rigidity had improved remarkably, and by September 17 she was able to walk with help. She was discharged on September 18, and was in good health when seen on October 16.

Comment: This is a severe case of generalized tetanus in a girl, illustrating the shortcomings of Mephenesin both by vein and by mouth, and the usefulness of Avertin as a muscle relaxant in selected cases. This experience also emphasized that complete and permanent muscle relaxation cannot be attained until the growth and multiplication of the *Cl. tetani* are stopped and further production of toxin is prevented. Further administration of peni-

cillin by the intramuscular route would have been of doubtful benefit in the presence of a foreign body and on active infection in the portal of entry, aiding the growth of the *Cl. tetani*. The local injection of penicillin may have been of aid, but wide debridement with the removal of the foreign body was indicated from the outset. Both the Avertin and Mephenesin are useless if not used in conjunction with other measures. Tracheotomy was an absolute necessity from the outset.

Discussion

Although the number of cases studied is too small to warrant definite conclusions, certain observations are considered worthy of discussion. It appears that Mephenesin has a place in the management of certain cases of tetanus until a better and less toxic muscular relaxant is available.

Either partial or complete relaxation was obtained in all but two cases of our series when the drug was administered repeatedly intravenously in doses of 25 to 100 c.c. of 2 per cent solution, or when 100 to 300 c.c. of the solution, diluted in 500 c.c. of 5 per cent dextrose in water, were given at a rate of over 60 drops per minute. The amount of drug required depended on the severity of the condition and on individual tolerance.

The drug was useful as an emergency treatment for laryngeal spasms in six cases, and as a general muscular relaxant in combination with deep sedation in seven. In two instances the usual doses of Mephenesin failed to produce relaxation during tracheotomy. Since a local anesthetic was used in those two cases, it seems that rectal Avertin is a better anesthetic for that operation.

Twelve of the cases studied would have required either the continuous administration of variable doses of Mephenesin in 5 per cent dextrose in water, or the intravenous injection of 50 c.c. or more of the undiluted solution at intervals of two to three hours for the attainment of continuous muscular relaxation. Both methods were impractical because of the danger of thrombophlebitis. This observation emphasizes the time limitations of the effect of the drug, and illustrates the constant medical supervision required during its use.

Three patients developed thrombophlebitis of arm veins, and one of the leg veins, as a result of the administration of the drug. One had anesthesia of the buccal and pharyngeal mucosa on receiving the drug by mouth, this being one of the dangers of this method of administration.[2c] There were no instances of gross hemolysis or hemoglobinuria.[4] The drug failed to produce the expected beneficial effects in two patients (cases 6 and 15), and in both, muscular relaxation was attained only after the administration of tribromoethanol by rectum.

Our observations tend to show that no matter how effective in controlling muscle spasms, Mephenesin does not contribute to the prevention of pneumonia, and cannot take the place of tracheotomy in the management of tetanus.

The exact dosage of Mephenesin in severe tetanus is unknown. Each case has to be individualized. While one of our patients required a rate of infusion of over 75 drops per minute of 300 c.c. of a 2 per cent solution of Mephenesin dissolved in 500 c.c. of 5 per cent dextrose in water, another one was benefited by 60 drops of 100 c.c. in the same amount of diluent.

It is open to speculation whether a large initial intravenous dose may render the patient able to maintain continued muscular relaxation if given the drug in heavy doses orally, but in our limited experience we found no need for oral Mephenesin in the severe forms of the disease.

An ideal muscle relaxant in tetanus should be nontoxic, of lasting effects and easy to administer. A long search has led to the use of d-tubocurarine hydrochloride, with poor results. Its use is condemned because of its transitory and unpredictable effects, and because of the danger of respiratory depression and bronchial obstruction. The use of intravenous Pentothal Sodium is contraindicated in tetanus because its effect is transitory and there is always the danger of respiratory depression and perpetuation of the laryngeal spasms. The other drugs used are either too toxic or of very fleeting effect.[2a]

Rectal tribromoethanol (Avertin) in doses of 50 mg. per kilo of body weight every three to four hours has been found effective by some investigators, but it may cause respiratory depression and rectal irritation.[2a] Mephenesin has been found by several investigators to be beneficial in tetanus when administered intravenously or orally. Some of the toxic reactions, such as a sudden fall in blood pressure due to myocardial depression,[3] thrombophlebitis from local irritation,[2b] abdominal pain and anemia,[5] and hemolysis, occasionally accompanied by hemoglobinuria, have been mentioned.[4] Its administration in elixir or powder form has been condemned, unless given by stomach tube, because of its anesthetic effects on the buccal and pharyngeal mucosa, increasing the danger of aspiration not only of the drug but also of the secretions of the upper respiratory passages.[2c]

An accurate evaluation of the various methods of therapy is extremely difficult in a disease with such wide variations as tetanus. The low mortality rate of 13.3 per cent in this series, although suggestive, cannot be accepted without mental reservations, because of the smallness of the series. Mephenesin deserves a more extensive clinical trial as a muscle relaxant in tetanus. The drug is useful as an emergency treatment for laryngeal spasms, also during tracheotomy, if a local anesthetic is used, and as a general muscular relaxant in combination with deep sedation. It appears to be the drug of choice in mild or moderately severe tetanus, when convulsions are mild or infrequent. It does not act quickly in the severe form. When convulsions are frequent and severe, or when tetanus complicates serious cardiovascular ailments, frequent or continuous administration of the drug becomes necessary.

It must be emphasized that tetanus should be managed by a team of specialists, and not by the internist alone. With full coöperation from the general surgeon, the anesthetist and the otolaryngologist, the internist can now offer the patient with tetanus a better chance of survival.

Summary and Conclusions

Analysis has been made of the data collected in the clinical study of 15 patients with severe and moderately severe tetanus who were managed mainly as respiratory problems and who received Mephenesin as a muscular relaxant.

Although some variation in tolerance was observed, the intravenous administration of 50 c.c. of a 2 per cent solution of the drug secured muscular relaxation in 13 of the 15 cases.

Two cases required repeated doses of rectal tribromoethanol for efficient relaxation and the control of convulsions.

Observations on four patients who received the drug in doses of 100 to 300 c.c. of the 2 per cent solution, diluted in 500 c.c. of 5 per cent dextrose, suggest that prolonged muscular relaxation can be obtained at an intravenous infusion rate of over 60 drops per minute.

The drug was of great usefulness, and was probably life-saving, in the treatment of laryngeal spasms in six of the cases.

Mephenesin was useful as a muscular relaxant during tracheotomy done under local anesthesia in seven instances, and it was of little benefit in two.

The duration of the relaxing effect of the drug depended on the severity of the disease, the amount given, the method of administration and the individual tolerance.

Oral Mephenesin (6 gm. daily) was not effective as a relaxant in two cases.

Three patients developed thrombophlebitis of the arms, and one, of the leg veins.

One had anesthesia of the pharyngeal and buccal mucosa when the drug was given per os.

There were two deaths (13.3 per cent), one attributable to heart disease and the other directly to tetanus (6.6 per cent).

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PAROXYSMAL AURICULAR TACHYCARDIA: OBSERVATIONS IN 47 CASES*

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BECAUSE paroxysmal auricular tachycardia is rather commonly seen, because in at least some patients it creates a considerable degree of apprehension, because physicians themselves differ so in evaluating its prognosis, and because the author personally has this functional disorder, it was decided that some comments and observations could perhaps be profitably made regarding this subject. Forty-seven patients with paroxysmal auricular tachycardia seen in the author's private practice within the last few years have been studied in the preparation of this paper.

OBSERVATIONS

The criterion for diagnosis of paroxysmal auricular tachycardia on the included cases largely depends upon an accurate history of *sudden* onset and termination of rapid heart action of approximately twice normal rate with regular rhythm. Some of the patients gave a history indicative of extrasystoles preceding and following the tachycardia. Because the duration of the tachycardia most commonly is minutes or hours, and it was not always possible to see the patient during the actual attack, confirmation of the diagnosis by physical examination and electrocardiogram was not possible in the majority of cases. To the author, however, the history was sufficiently reliable to warrant the diagnosis in the included cases, and all cases of questionable validity were excluded.

Although paroxysmal auricular tachycardia has been reported to occur more frequently in males, in the present series there were 21 males and 26 females. The earliest age of onset in the included cases was eight years and the oldest included was 58 years, the average age of onset being 29 years. The onset was below the age of 30 in 25 cases and above the age of 50 in only four cases. The average duration of interval between the initial episode of paroxysmal auricular tachycardia and the latest follow-up on the included cases was 12 years. Of the cases in which the heart rate was definitely known during the tachycardia, the slowest rate was 136/min. and the most rapid rate was 220/min. These 47 cases represent a incidence of approximately 1 per cent of the patients seen during this interval.

Various stimulating factors definitely predisposed to paroxysmal auricular tachycardia in the cases studied. Sudden changes in body position in which the heart is thrown toward the anterior chest wall as in stooping

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over, blows to the precordium as from an ocean wave hitting the chest while the patient is swimming or from a boxing blow, excitement and emotional states, fatigue and, at least in some patients, excessive use of alcohol, tobacco and coffee predisposed to the onset of the tachycardia. It was of interest, however, that of 47 patients asked, 22 denied using alcohol and 23 denied using tobacco, 15 of these using neither, not because of effect upon the paroxysmal auricular tachycardia but because of personal preference. Another three of these patients had to give up drinking and two to give up smoking because these precipitated their tachycardias. Two patients volunteered the information that their attacks of paroxysmal tachycardia were more frequent near the time of menses.

The paroxysmal auricular tachycardia rate was quite consistent for the same individual with repeated occurrences. Eight patients seen repeatedly during the tachycardia always had their same predictable rate, and the author has observed this in himself for 20 years. Associated with the tachycardia were feelings of fullness or heaviness in the chest, in a few instances associated with vague precordial pain and distress, severe in one case and moderate in intensity in another. A feeling of air hunger was not uncommon during the tachycardia, and symptoms of a superimposed hyperventilation syndrome occurred in two. As far as associated organic heart disease or injury to the myocardium is concerned, only four patients in this group had associated hypertension, only two of whom showed definite evidence of myocardial involvement.

Case Reports

Case 1. A white woman, age 41 (blood pressure, 186/120 mm. of Hg in upper extremities), had coarctation of the aorta with myocardial enlargement and had had paroxysmal auricular tachycardia at intervals since she was 25 years old. In this patient acute pulmonary edema was precipitated by the tachycardia. Electrocardiogram showed left axis deviation, QRS interval of 0.10 second, and T wave inversion immediately after the paroxysmal auricular tachycardia. Quinidine controlled the tachycardia quite successfully, pulmonary edema then subsiding and T waves subsequently gradually reverting toward normal upright. This patient declined surgery for her coarctation.

Case 2. A white man, age 51 (blood pressure, 180/100 mm. of Hg), had had paroxysmal auricular tachycardia at intervals since the age of 40, tolerated well until recently. On one occasion the patient required a total divided dose of 3.2 gm. quinidine in 24 hours before reversion to normal sinus rhythm. On another occasion this patient was seen in a definitely shocklike state after two days of tachycardia, with blood pressure of 106/10 mm. of Hg. On his worst episode, three days of paroxysmal auricular tachycardia at a rate of 212/min. precipitated acute pulmonary edema and congestive heart failure. This patient had cardiac enlargement, and an electrocardiogram showed a tendency to left axis deviation, T wave inversion and frequent ventricular extrasystoles after cessation of the tachycardia. Digitoxin effectively reverted the tachycardia to normal sinus rhythm, with clearing of the shock-like state and of the congestive failure.

Case 3. A white woman, age 62 (blood pressure, 160/94 mm. of Hg), had had paroxysmal auricular tachycardia at intervals since she was eight years old, a period

of 54 years, the longest interval of any patient in this series. Heart examination between episodes of tachycardia was normal, and electrocardiogram showed only a tendency to left axis deviation. She well tolerated her paroxysmal auricular tachycardia, which always stopped spontaneously within a few hours or less.

Case 4. A white male, age 42 (blood pressure, 204/124 mm. of Hg), had had a history of paroxysmal auricular tachycardia at intervals for the last year. Heart examination was normal between episodes of tachycardia, and electrocardiogram was normal except for a tendency to left axis deviation. Tachycardia was well tolerated and returned to normal rhythm with vagus stimulation by carotid sinus pressure.

None of the other 43 cases showed any evidence by history or physical findings of organic heart disease. Electrocardiograms showed typical Wolff-Parkinson-White patterns (short PR interval and prolonged QRS) in five cases. Three other cases showed normal PR intervals of 0.16 second, with QRS intervals of 0.10 to 0.11 second. The patient with the coarctation, the fourth case with QRS interval of 0.10 to 0.11 second, was the only one of this group with evidence of organic heart disease. Ages of the other three patients (all males) at the time of first detection of normal PR intervals and QRS intervals of 0.10 to 0.11 second were 24, 27 and 45. T wave inversion immediately after an episode of paroxysmal auricular tachycardia with subsequent reversion to normal was seen in two other cases. A-V nodal and/or ventricular extrasystoles were seen in three other cases in which digitalis and its glycosides were omitted. In 24 of these patients electrocardiograms were entirely normal between episodes of tachycardia. Electrocardiograms were not made for the remaining six patients.

Not related to and not occurring at the time of paroxysmal auricular tachycardia, postural hypotension was found in one of the present cases. Another case is of special interest not because of any evidence of organic heart disease but because of other complications which may or may not be related to the paroxysmal auricular tachycardia.

Case 5. A white man, age 49, had had a history of episodes of paroxysmal auricular tachycardia since the age of 32. He was markedly psychoneurotic and paranoid, and was first seen by the author in consultation after the present episode of paroxysmal auricular tachycardia had lasted seven days with a rate of 207/min. At that time he also had thrombosed hemorrhoids, with extension of the thromboses palpable on rectal examination, indicating pelvic phlebothrombosis, and pulmonary embolism and infarctions. He had a further complication of pulmonary tuberculosis. Digitalis failed to revert the rhythm to normal. Quinidine and morphine failed on this occasion, although in numerous subsequent episodes they were successful some of the time. Mecholyl successfully converted the rhythm to normal and was by far the most effective drug in this patient, although he rebelled against its use because of its well known side effects.

Second only in frequency of occurrence to the feeling of the paroxysmal tachycardia in these patients are anxiety and apprehension, as is easily understood by one who has this type of tachycardia. Only 10 of the 47 patients showed no evidence of this at the time of the examination. Twenty-two of these patients had a definite anxiety state, mild in five, and 15 others had

definite psychoneurosis with anxiety features. Globus hystericus was not uncommonly associated.

Twenty-three of the 47 patients studied had associated gastrointestinal tract symptoms, consisting of upper abdominal fullness and distention, nausea, vomiting and/or belching, worse during the tachycardia. Two of the patients had had diarrhea on multiple occasions, but in each instance this followed rather large doses of quinidine. Two of the patients recalled that spontaneous vomiting had resulted in cessation of the tachycardia on some occasions. Several more had induced gagging and vomiting with the same beneficial results, occasionally with failure to stop the tachycardia.

Although every patient was not specifically asked, four volunteered the history that during the paroxysms of tachycardia there was a greatly increased frequency and volume of urination, indicating that at least in some patients with healthy myocardia there was increased rather than diminished blood flow during the tachycardia. Evidence of diminished blood flow during the tachycardia occurred in the first two cases summarized above, and in two others who fainted while forcibly maintaining the upright posture during the tachycardia.

One healthy woman gave a history of paroxysmal auricular tachycardia beginning at the age of 30 and recurring at intervals until she was 50, with no recurrence at all for the next 10 years. With the exception of the above-mentioned cases the course of the tachycardia was benign in all instances, the tachycardia in the vast majority stopping spontaneously after only a short time or after carotid sinus pressure, prolonged forced deep inspiration with pressure against a closed glottis, or spontaneous or induced vomiting or gagging as mentioned above.

Reassurance and explanation were considered the most important things for the patient in the vast majority of instances, and in only seven of the 47 patients were drugs given to control or stop the tachycardia. These seven patients, however, were seen in numerous recurrences of the tachycardia, in two of the patients as many as 10 times each. Whereas the slower acting digitalis failed in the only case in which it was tried, the more rapidly acting digitoxin was successful in each of five trials. Six of the patients received quinidine, in three with complete success, and in the other three with moderate success, stopping some but not all episodes of tachycardia. Mecholyl was used in three patients, more effectively than anything else in one and failing in one. Well known side reactions, however, keep this from being the drug of choice. Administration of morphine in four instances was followed by normal sinus rhythm, but the paroxysmal auricular tachycardia persisted in two other instances in which it was tried.

Discussion

It is obvious that a series of only 47 cases is too small to solve all unanswered questions regarding paroxysmal auricular tachycardia, and that

this type of paper regarding clinical features adds nothing to the present knowledge of the physiologic mechanism of this disorder. Wolferth and Wood, Butterworth and Poindexter, Wilson, Rosenbaum, Prinzmetal and others have made definite contributions to the latter. Aberrant atrioventricular conduction with normal PR interval and prolonged QRS complex simulating bundle branch block, as occurred in several patients in this series with paroxysmal tachycardia, has previously been reported.[4]

Consideration of these 47 cases along with other reports in the literature, however, may help to shed some light on the clinical features and prognosis of this disorder. The high incidence of associated psychoneurosis and anxiety has previously been observed, and it is well known that at times they have been made worse when doctors rendered an undeservedly poor prognosis to the patient, particularly after misinterpretation of the Wolff-Parkinson-White type of electrocardiogram. The rôle of the autonomic nervous system in this disorder seems apparent.

A previously reported incidence of syncopal attacks during paroxysmal auricular tachycardia of about 4 per cent seems confirmed by two similar experiences in this series.[9]

Although the author is unaware of any good studies of circulation time in patients with paroxysmal auricular tachycardia, because of definite polyuria experienced by him and reported by other patients during the tachycardia it is his definite impression that many patients with paroxysmal auricular tachycardia have increased rather than diminished circulation. This would be particularly true in young, otherwise healthy adults with relatively slow tachycardia rates (150/min. or less) and without extensively prolonged tachycardia. Exceptions, of course, are those patients, older, hypertensive, or with organic heart disease, in whom congestive failure or shock is precipitated by a rather prolonged interval of tachycardia of rapid rates (200 +/min.).

Other exceptions are infants, in whom the diagnosis of paroxysmal auricular tachycardia is based upon the findings of sudden onset of weakness, restlessness, fretfulness, listlessness, drowsiness or wakefulness, vomiting, refusal to nurse, rapid respiration, cyanosis, pallor, cold clammy sweat, fever, leukocytosis, tachycardia, and signs of congestive heart failure. The prognosis is obviously worse than in healthy adults, congestive heart failure or shock being the rule when the diagnosis is established in infancy. A disproportionately large number of infant deaths associated with paroxysmal auricular tachycardia have been reported. This may be because only prolonged episodes of the tachycardia are accurately diagnosed during infancy, or it may be due to some quality of the infant's myocardium which makes it more difficult to tolerate the tachycardia. The latter seems indicated by the finding of rhabdomyoma of the heart on postmortem examinations of at least three infants with paroxysmal auricular tachycardia, two as previously reported and one seen locally.[6] Two other infants with paroxysmal auricular tachycardia have died locally in the last few years.[10]

In addition to digitalis, digitoxin, quinidine, Mecholyl and morphine, other drugs reported most effective in stopping paroxysmal auricular tachycardia include lanatoside C,[3] Neosynephrine,[16] neostigmine,[14] acetylcholine [11] and intravenous magnesium sulfate.[17] Quick acting digitalis glycosides probably are generally considered best for stopping this tachycardia, and quinidine best for preventing it.

The total number of deaths reported in the literature from paroxysmal auricular tachycardia is surprisingly small considering the relatively frequent incidence of this disorder, and the relationship between the deaths and the tachycardia is far from proved in some instances.[1, 2, 7, 8, 11] The lack of association of paroxysmal auricular tachycardia and death from myocardial infarction has been commented upon.[12] The vast majority of reports commenting on prognosis in this disorder in adults are favorable. One case has been reported [18] of paroxysmal auricular tachycardia with block present almost continuously for 25 years in a patient then 79 years old, with no ill effect upon the health of the individual. This patient also had right bundle branch block (or a variant of the Wolff-Parkinson-White syndrome, with normal PR and prolonged QRS) for 25 years, indicating the possible benignity of this finding. Another case, of a 70 year old woman with myocardial infarction superimposed upon the Wolff-Parkinson-White syndrome with a smooth, uncomplicated recovery, emphasized the favorable outlook of this abnormality.[5] Wolff and White conclude: "The clinical course of those who coincidentally acquired heart disease does not appear to be altered by the abnormal electrocardiogram or by an unusual propensity to paroxysmal tachycardia." [18]

In the present series thus far the prognosis has been excellent in all except the cases with hypertensive heart disease and coarctation of the aorta, complications not caused by the paroxysmal auricular tachycardia, although the latter definitely precipitated congestive heart failure in their presence. These patients would undoubtedly have gone into congestive failure in the not too distant future, however, even if they had not had paroxysmal auricular tachycardia, because of the myocardial changes caused by their primary diseases. Although the prognosis seems bad in infants without proper treatment, in adults without coincidentally acquired organic heart disease the prognosis would seem quite good. The total number of deaths in adults reported in the literature is perhaps no greater than would be anticipated in an equal number of individuals without paroxysmal auricular tachycardia, on the basis of its frequency of occurrence.

Conclusions

Paroxysmal auricular tachycardia as seen in 47 cases in the author's private practice has been summarized. These cases include five patients with the Wolff-Parkinson-White syndrome, and four others with a probable variant of the same.

The high associated incidence of anxiety states is noted. Reassurance and explanation were considered the most important things to be done for the majority of patients.

In only seven of 47 patients was specific medication necessary. In these the quick acting digitalis glycosides seemed the drug of choice in stopping the tachycardia in most instances. Quinidine was the best preventive.

Except in untreated patients in infancy and in people with coincidentally acquired heart disease the prognosis would seem good. Of the only two patients showing definite myocardial disease in this series, one had coarctation of the aorta and the other hypertensive heart disease.

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DIABETES MELLITUS AMONG INDIANS OF THE AMERICAN SOUTHWEST: ITS PREVALENCE AND CLINICAL CHARACTERISTICS IN A HOSPITALIZED POPULATION*

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INVESTIGATORS engaged in long-term studies of chronic and degenerative illnesses have documented the practicability of control of a wide variety of such disorders.[1] In common with individuals suffering from certain other of these ailments, the patient with diabetes mellitus has realized the dividends accruing from early detection and inauguration of treatment. Prolonged and aggressive control following discovery of diabetes in its earliest stages has resulted in a material reduction in the incidence of complicating effects in retinal, renal and peripheral vascular areas.[2-6] Intensive case-finding programs, "diabetes fairs" and community surveys by the medical profession in coöperation with federal, state and local agencies have disclosed that diabetes is much more prevalent than is commonly supposed.[7, 8]

In certain of the United States, notably in the Southwest, the American Indian forms a considerable portion of the aggregate population, yet little information exists concerning the prevalence of diabetes in this group. For example, in an early evaluation it was considered that "diabetes and appendicitis are of relatively rare occurrence." [9] Some years later, Joslin, in an address entitled "The Universality of Diabetes," commented upon an exhaustive personal survey: "The number of Indians with diabetes in Arizona bore essentially the same relative proportion, 10 per cent, as do Indians to the total population. Diabetes in Arizona is just as common among Indians as among the rest of the population." [10] The rarity of diabetes among Navajos and its prevalence among Pimas were noteworthy in Joslin's evaluation. Salsbury was able to discover only five diabetics among 25,000 Navajos admitted to an Arizona Mission hospital, and stated that "blood chemistries done on a large number of Navajo patients show an average blood sugar of approximately 90 mg. per cent against a normal in white people of approximately 120 mg. per cent." [11] In a comprehensive unpublished tabulation of 7,989 discharges from Bureau of Indian Affairs hospitals in Arizona, Utah and Nevada, Lull recorded a total of 126 diabetic discharges; attention was directed to the prevalence of diabetes among Pima and Colorado River Indians, in contrast to its infrequency among Apaches, whose reservation bordered that of the Navajos.[12]

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Because of the fragmentary nature of the data available dealing with prevalence of diabetes among American Indians, an attempt was made to assess its incidence among admissions to hospitals dealing exclusively with their care, and to determine whether its clinical characteristics differentiate it from the disorder as it is known in non-Indian populations.

Methods

The Phoenix Area of the Bureau of Indian Affairs includes 36,000 Indians resident in the states of Arizona, Utah and Nevada, and is exclusive of the Hopi and Navajo reservation population. There are nine Indian Field Service Hospitals in the Area, each located upon a reservation and providing medical care for a separate tribal unit, although there may be a very small percentage admixture of Indians of other tribes. In addition, a separate facility, the Phoenix Medical Center, located in Phoenix, Arizona, and not on a reservation, acts as a referral center for patients requiring further consultative, diagnostic and therapeutic assistance; the tribes represented are, accordingly, varied.

From July 1, 1950, to June 30, 1952, the two year period covered by this report, there were 16,296 consecutive admissions to hospital facilities of the Phoenix Area of the Bureau of Indian Affairs. The hospital admission rate for diabetes mellitus was determined.* Because of geographic limitations precluding detailed review of the records of cases of diabetes at the various Field Service Hospitals, it was decided to submit to further scrutiny the records of diabetics among the 2,008 admissions to all services of the Phoenix Medical Center, to determine, if possible, the natural history of the disorder among the Indian population. The diagnosis in each case conformed to the criteria of the American Diabetes Association.[18]

Results

A. Prevalence by Sex and Tribal Units: Table 1 presents the prevalence of diabetes mellitus among 16,296 admissions to the medical facilities of the Phoenix Area for a two year period tabulated by sex of patient and tribal units served. There were 256 diabetic admissions, an over-all case-admission rate of 1.5 per cent for the entire area. There were 105 male diabetics among 7,030 male admissions, an admission rate of 1.4 per cent, and 151 female diabetics among 9,266 female admissions, an admission rate of 1.6 per cent. Diabetic admissions were most frequent among Yuma men, Pima men and women, and Mojave (Colorado River Tribes) men, and least frequent among Apache men and women, Papago women, and Paiute and Shoshone women admitted to the Western Shoshone reservation hospital. Prevalence by tribal groups was greatest among Pimas, Yumas and Mojaves, and least among Papagos, Apaches, and Paiutes and Shoshones admitted to

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the Western Shoshone hospital. There were 2,008 consecutive admissions to the Phoenix Medical Center during this period, a mosaic of 44 different tribal groups; there were 63 diabetic admissions, a case admission rate of 3.1 per cent. The diabetic case admission rate for men was 1.8 per cent and for women 4.2 per cent. The diverse and unequal tribal representation makes assessment of tribal prevalence of diabetes of doubtful statistical validity in the relatively limited hospital population of the Medical Center. It should be noted, however, that the diabetic case admission rates for the three largest tribal groups, Hopis and Navajos, Apaches and Pimas, comprising almost 65 per cent of all admissions to the Medical Center, were 0.6 per cent, 1.6 per cent and 6.7 per cent, respectively.

B. Clinical Characteristics: Attention was directed next to a review of the records of all diabetic admissions to the Phoenix Medical Center. The

TABLE I

Prevalence of Diabetes Mellitus by Sex and Tribe among 16,296 Indians Admitted to Hospital Facilities over a Two Year Period

Agency	Principal Tribe Served	Total No. Admitted			No. Diabetics Admitted			% of Diabetic Admiss.		
		Male	Female	Total	Male	Female	Total	Male	Female	Total
Walker River	Paiute & Shoshone	717	968	1685	8	10	18	1.1	1.0	1.0
Western Shoshone	Paiute & Shoshone	390	361	751	3	0	3	0.7	0.0	0.3
Colorado River	Mojave	611	816	1427	18	14	32	2.9	1.7	2.2
Fort Yuma	Yuma	221	256	477	10	5	15	4.5	1.9	3.1
Pima	Pima	1152	1746	2898	32	62	94	2.7	3.5	3.2
San Xavier	Papago	723	1181	1904	6	2	8	0.8	0.1	0.4
San Carlos	Apache	932	1171	2103	2	7	9	0.2	0.5	0.4
Fort Apache	Apache	1017	1149	2266	3	0	3	0.2	0.0	0.1
Uintah and Ouray	Ute	331	546	877	6	5	11	1.8	0.9	1.2
Total all Field Hospitals, Phoenix Area		6094	8194	14,288	88	105	193	1.3	1.2	1.3
Phoenix Medical Center Hospital		817	930	1747	13	23	36	1.5	2.4	2.0
Phoenix Medical Center Sanatorium		119	142	261	4	23	27	3.3	16.1	10.3
Total all Hospitals, Phoenix Area, B.I.A.		7030	9266	16,296	105	151	256	1.4	1.6	1.5

Medical Center consists of two units: the Hospital, which is the general medical facility, and the Sanatorium, which is devoted to the care of patients with tuberculosis. Preliminary appraisal indicated the desirability of evaluating separately diabetic patients admitted to these two units.

1. Prevalence by Age and Sex (table 2): There were 36 diabetic admissions to the Hospital, a case admission rate of 2.0 per cent; there were 27 diabetic admissions to the Sanatorium, a case admission rate of 10.3 per cent. At both institutions diabetic admissions were more frequent among women than among men; however, diabetes was more prevalent among tuberculous men than among nontuberculous women (prevalence: tuberculous women > tuberculous men > nontuberculous women > nontuberculous men). No diabetic under 20 years of age was seen at either division despite the relatively large number of admissions in the younger age groups. There was an irregular but definite increase in prevalence of this disorder with

TABLE II

Incidence of Diabetes Mellitus among 2,008 Indian Admissions to the Phoenix Medical Center by Age and Sex

A. Phoenix Medical Center Hospital

Age	Total Male Admissions	Male Diabetics	%	Total Female Admissions	Female Diabetics	%
0–9	328	0	0	279	0	0
10–19	174	0	0	175	0	0
20–29	77	2	2.6	226	5	2.2
30–39	47	4	8.5	120	0	0
40–49	57	4	7.0	65	5	7.6
50–59	58	1	1.7	35	4	11.4
60–69	48	2	4.1	21	5	23.8
70–79	27	0	0	17	4	23.5
80 and above	1	0	0	2	0	0
Totals	817	13	1.5	930	23	2.4

B. Phoenix Medical Center Sanatorium

0–9	15	0	0	14	0	0
10–19	37	0	0	30	0	0
20–29	40	0	0	34	1	2.9
30–39	9	1	11	22	3	13.6
40–49	4	1	25	26	14	53.8
50–59	6	2	33	11	5	45.4
60–69	8	0	0	3	0	0
70–79	0	0	0	2	0	0
80 and above	0	0	0	0	0	0
Totals	119	4	3.3	142	23	16.1

increasing age among all tuberculous patients and nontuberculous women, while a decrease was noted among nontuberculous men over the age of 50.

2. Age at Initial Admission: Fourteen tuberculous diabetics were admitted a total of 27 times, and 32 nontuberculous diabetics were admitted a total of 36 times. The ages of these patients at their initial hospitalization

TABLE III

Age at Initial Admission of 46 Diabetic Indians to the Phoenix Medical Center, 1950–52

Age	Medical Center Hospital			Medical Center Sanatorium		
	Male	Female	Total	Male	Female	Total
0–9	0	0	0	0	0	0
10–19	0	0	0	0	0	0
20–29	1	5	6	0	1	1
30–39	3	0	3	1	1	2
40–49	4	4	8	1	7	8
50–59	1	4	5	1	2	3
60–69	2	4	6	0	0	0
70–79	0	4	4	0	0	0
80 and above	0	0	0	0	0	0
	11	21	32	3	11	14

are presented in table 3. The largest number of diabetic admissions to both divisions was first seen in the fifth and sixth decades of life. Almost one third of the nontuberculous diabetics were seen for the first time at age 60 or above, whereas no tuberculous diabetic was seen initially during this period of life.

3. Duration of Known Diabetes: The known duration of the diabetic process could be approximated for both groups (table 4), most of whom had

TABLE IV

Known Duration of Diabetes Mellitus among 46 Indians Admitted to the Phoenix Medical Center

Years Known Duration	Medical Center Hospital			Medical Center Sanatorium		
	Male	Female	Total	Male	Female	Total
Less than 1 to 5	3	6	9	2	4	6
6–10	1	5	6	0	3	3
11–15	2	2	4	1	0	1
16–20	0	0	0	0	0	0
Discovered on entry	5	8	13	0	4	4
	11	21	32	3	11	14

known of their disease for less than 10 years. Diabetes was unknown prior to entry in 40.6 per cent of the Hospital diabetics and in 28.5 per cent of the Sanatorium diabetics.

4. Age at Onset: The ages of these 46 diabetics at the time of discovery of their disease could be determined (table 5). Known onset occurred prior to 40 years of age in almost one-half of tuberculous diabetics and in slightly over one third of nontuberculous diabetics. The lesser frequency of onset below age 40 in the Hospital diabetics seemed largely a reflection

TABLE V

Age at Known Onset of Disease among 46 Indians with Diabetes Mellitus Admitted to Phoenix Medical Center

Age	Medical Center Hospital			Medical Center Sanatorium		
	Male	Female	Total	Male	Female	Total
0–9	0	0	0	0	0	0
10–19	0	1	1	0	0	0
20–29	4	4	8	1	1	2
30–39	1	1	2	0	4	4
40–49	3	6	9	1	5	6
50–59	1	3	4	1	1	2
60–69	2	5	7	0	0	0
70–79	0	1	1	0	0	0
80 and above	0	0	0	0	0	0
Totals	11	21	32	3	11	14

of the later onset of the disease in the female patients, who comprised two thirds of this group.

5. Severity of Diabetes: While hospitalized, all tuberculous diabetics required insulin therapy in addition to dietary management, while one fourth of the nontuberculous diabetics could be controlled by diet alone (table 6). The majority (71.4 per cent) of the tuberculous patients could be classed as having severe diabetes, as compared with the minority of the nontuberculous patients.

6. Presence of Obesity: In every instance a description of the habitus of the patient was recorded, in addition to conventional measurements of

TABLE VI

Severity of Diabetes Mellitus among 46 Indian Patients

	Medical Center Hospital	Medical Center Sanatorium
Mild (no insulin required)	8	0
Moderate (1–20 units insulin)	7	1
Moderately severe (21–50 units insulin)	13	3
Severe (51 or more units insulin)	4	10
	32	14

height and weight. Obesity was considered to be present if weight varied more than 10 per cent above the ideal weight of a normally built person of the same height and sex at age 30 to 35 years.[14] Approximately 30 per cent of all nontuberculous and 7 per cent of all tuberculous diabetics were regarded as obese by this criterion.

7. Complications: The frequency of occurrence of conditions complicating diabetes was tabulated for these 46 patients (table 7). Nephropathy, pyelonephritis, retinitis, hypertension, congestive heart failure and gangrene were the most common of the complications seen in the nontuberculous diabetics. Hypertension, retinitis, neuritis and calcified vessels were the most prominent complications in the diabetic with tuberculosis. No patient

TABLE VII

Complicating Conditions in Indian Diabetics, Listed in Descending Order of Frequency

A. Hospital Diabetics	B. Sanatorium Diabetics
1. Nephropathy	1. Hypertension
2. Pyelonephritis	2. Retinitis
3. Retinitis	3. Peripheral neuritis
4. Hypertension	4. Calcified vessels
5. Congestive heart failure	5. Nephropathy
6. Cataracts	6. Cataracts
7. Gangrene	7. Pyelonephritis
8. Coronary occlusion	8. Congestive heart failure
9. Hepatomegaly	9. Hypoglycemic reactions
10. Peripheral neuritis	
11. Calcified vessels	
12. Hypoglycemic reactions	
13. Osteomyelitis	

in either group had experienced an episode of diabetic coma. In both groups the number of complications rose with increasing known duration of disease (table 8).

8. Obstetrical History: Thirteen (61.9 per cent) of the nontuberculous and three (27.2 per cent) of the tuberculous diabetic women had never conceived. Miscarriages and stillbirths characterized the obstetrical background of the tuberculous diabetics who were able to conceive (table 9).

TABLE VIII

Number of Complicating Conditions per Patient among Indian Diabetics Tabulated According to Known Duration of Disease

Known Duration of Disease	A. Hospital Diabetics	B. Sanatorium Diabetics
1. Discovered on admission	0.76	0.00
2. Less than 1 year	0.66	0.00
3. From 1 to 5 years, inclusive	2.83	1.40
4. From 6 to 10 years, inclusive	3.00	3.33
5. From 11 to 15 years, inclusive	4.50	5.00

9. Reasons for Admission: Fourteen patients (43.7 per cent) admitted to the Medical Center Hospital presented themselves primarily for the treatment of diabetes or its complicating conditions (table 10). Diabetic nephropathy, congestive heart failure and cataracts were the most prominent of these problems. Only two patients were admitted for the regulation of their diabetic state. Symptoms referable to the hepatobiliary tree and orthopedic difficulties were of importance in the patients whose diabetic status

TABLE IX

Obstetrical History of 32 Indian Women with Diabetes

	A. Hospital Diabetics	B. Sanatorium Diabetics
1. Infertile	13	3
2. Pregnancies	31 (8 patients)	44 (8 patients)
a. Miscarriages	0	4
b. Stillbirths	0	5
c. Viable offspring	31	35

was incidental to their presenting complaints. All diabetics entering the Sanatorium were hospitalized because of active pulmonary tuberculosis.

10. Surgical Procedures: No surgical operation was performed on any of the diabetic patients with tuberculosis. Fifteen procedures were performed on as many nontuberculous diabetics (table 11). There was a single operative fatality in this latter group, representing a surgical mortality of 6.6 per cent.

11. Deaths: In addition to the lone operative fatality previously cited, there were two additional deaths in this series, both in patients with diabetes

of long duration who were suffering from congestive heart failure and renal insufficiency. The death rate was, accordingly, 6.6 per cent for the Hospital diabetics undergoing surgery of all kinds, 9.5 per cent for the Hospital diabetics treated medically, 8.3 per cent for all Hospital diabetics, and 4.4 per cent for all diabetic admissions to the Phoenix Medical Center,

TABLE X

Reasons for Admission of Diabetics to the Phoenix Medical Center Hospital

Reason for Admission	Admissions
1. Surgical procedures	15
2. Hepatobiliary disease	4
3. Rheumatoid arthritis	2
4. Iritis	2
5. Typhoid fever	1
6. Pneumococcal pneumonia	1
7. Primary syphilis	1
8. Congestive failure and diabetic nephropathy	5
9. Regulation of diabetes	2
10. Diabetic neuropathy	1
11. Diabetic ulcers	1
12. Carcinoma of the uterus	1
	36

since no deaths occurred in the Sanatorium patients during the period of study.

12. Severity of Tuberculosis: Of the 14 diabetic patients admitted to the Sanatorium, only one had minimal pulmonary tuberculosis, according to standard classification [15] (table 12). Two of the remaining cases (14.2

TABLE XI

Surgical Procedures Performed on Hospital Diabetics

Procedure	Number
1. Cholecystectomy	2
2. Orthopedic surgery	5
3. Ocular surgery	6
4. Repair of umbilical hernia	1
5. Appendectomy	1
	15

per cent) were moderately advanced, while the majority (78.5 per cent) had far advanced disease. In half of these patients the discovery of tuberculosis followed the diagnosis of diabetes; in five patients the diagnosis of tuberculosis antedated the detection of diabetes, and in two patients the two diseases were discovered simultaneously.

TABLE XII

Severity of Tuberculosis among 14 Indians with Diabetes

1. Minimal disease	1 (7.1%)
2. Moderately advanced disease	2 (14.2%)
3. Far advanced disease	11 (78.5%)

13. Family History of Diabetes: Two patients, both women admitted to the Hospital, gave a positive family history of diabetes, each having a single parent with the disorder. Two of the Hospital diabetics were man and wife.

Discussion

The observations of Joslin,[10] cited above, bear considerable evidence for the thesis that diabetes is universal. Further testing of discrete racial or national groups has been suggested to implement the scanty existing data favoring the universality of this disease.[7] The selection of relatively "pure" samples of various cultures has been hampered by intermarriage and the limited numbers available for such examination. In the Southwestern United States the American Indian, living largely a reservation existence, still provides a relatively homogeneous population for study.

Methods of evaluating the natural history of a disease in a hypothetic population have been summarized with lucidity by Dorn [16] in a recent presentation in which it is concluded that the extensive population survey complemented by the intensive longitudinal study of a complete population is the most satisfactory approach to the study of morbidity. Unfortunately, in the present study necessity, imposed by technical [17] and geographic limitations, has led to the less precise analysis of data assembled entirely from records of hospitalized individuals. That certain of the pitfalls inherent in the use of this method may be obviated by the collection of such statistics in an area in which a background of population figures is available is recognized by Dorn. It is realized, however, that hospital records deal with only a segment of the illnesses which developed during the period of study in this population, and with only a selected group of the population itself, i.e., those ill enough to require hospitalization for one reason or another.

The present evaluation deals with the prevalence of diabetes mellitus among 16,296 Indians admitted during a two year period to hospital facilities of the Bureau of Indian Affairs in the states of Utah, Nevada and Arizona; the total Indian census of this area, excluding the Hopi and Navajo reservation populations, was approximately 36,000 individuals. For the entire hospitalized population the prevalence of diabetes was 1.5 per cent, a figure roughly comparable to the 1.7 per cent incidence of this disorder detected by Wilkerson and Krall's now classic observations in a typical New England town.[7] The prevalence of diabetes among women (1.6 per cent) was slightly greater than among men (1.4 per cent).

When the prevalence of diabetes was assessed by tribal units, a unique circumstance made possible by the nature of reservation medical service, a striking difference in incidence was apparent. Diabetes was most prevalent among Pimas, Yumas and Mojaves, all tribes residing in recently-irrigated, low-altitude areas of high average year-round temperatures. In addition, the incidence of obesity among these tribes is relatively high as compared with a low incidence among Apaches, Paiutes and Shoshones. The latter

tribes reside in high-altitude plains and timberlands, and diabetes was infrequent in admissions to hospitals on their reservations. The Apache reservation is geographically adjacent to that of the Navajos, a group previously remarked for their low prevalence of this disorder.[11] The freedom from diabetes of the Papago Indian, who shares a common environment with the tribes of highest prevalence, is a subject for speculation, but may, in part, find its origin in the less sedentary habits of this group. Joslin has made note of this disparity, remarking: "Navajos are nomads, and the Apaches herdsmen, and the Pimas depend on agriculture and harvest their crops on shares, allowing the Papagos to do most of the work." [10]

The clinical characteristics of diabetes in Indians, as observed in the case histories of 63 diabetics admitted to the Phoenix Medical Center, conformed in most respects to the disorder as it is recognized in non-Indian populations. The incidence rose, irregularly but definitely, with increasing age. A large minority had been unaware of their disease prior to hospitalization. Degenerative vascular lesions were common, and their incidence paralleled the known duration of diabetes. Correlation with degree of metabolic control was not possible because none of the known diabetics had observed dietary instructions or taken insulin prior to re-admission, in spite of active education in their disease at an earlier visit. It should be emphasized that language difficulties, geographic inaccessibility, total absence of home sanitary facilities and limitations of personnel, often in combination, pose problems in the treatment of the average Indian diabetic differing in scope and degree from those encountered by physicians in non-Indian practice. In addition to the variety of degenerative complications observed in these Indian patients, the data tabulated indicate that infertility was common in the diabetic female, and pregnancy results in fetal and infantile loss roughly comparable to that seen in non-Indian diabetic women.[18]

Several features in this study were of special interest. First, no Indian patient under the age of 20 was found to have diabetes mellitus. Second, no Indian was seen in diabetic coma at the Phoenix Medical Center or at any of the Field Service Hospitals. Third, admissions for the purpose of metabolic regulation were infrequent, comprising only 5.5 per cent of all diabetic entries into the Medical Center Hospital. In the above respects, diabetes in the Indians observed seemed to resemble the "maturity onset" type of this disorder described by others as occurring in middle aged obese individuals with moderately reduced available plasma [19] and extractable pancreatic [20] insulin. Obesity was indeed common among the Hospital diabetics, although it was infrequent among Sanatorium diabetics, most of whom gave evidence of constitutional reaction to their far-advanced tuberculous disease.

Certain aspects of diabetes among Indians with tuberculosis are worthy of comment. The coincidence of these two diseases in non-Indian populations has been reviewed recently by Speck and associates,[21] whose own ex-

perience included seven cases (3.4 per cent) of tuberculosis in 205 diabetic clinic patients, and 15 cases (0.63 per cent) of diabetes among 2,366 admissions to a tuberculosis hospital. In our evaluation, diabetes occurred five times more frequently among tuberculous (10.3 per cent) than among non-tuberculous (2.0 per cent) Indian patients. The lesser frequency of obesity and the greater severity of diabetes among tuberculous Indians may be a reflection of the well known additive effect of a severe infection on a relatively mild metabolic derangement. Diabetes was discovered prior to the diagnosis of tuberculosis in half, and the extent of the pulmonary process was of moderate to far advanced degree in almost all, corroborating the observations of Ferrara [22] in a non-Indian tuberculous hospital population. The slightly lower incidence of degenerative complications in tuberculous diabetics may be a reflection of the prolonged previous periods of hospitalization for the treatment of tuberculosis in some of these patients, with its attendant metabolic control, as contrasted with the complete lack of control noted in the Hospital patients with diabetes known prior to re-admission.

Summary and Conclusions

The prevalence of diabetes mellitus was determined among 16,296 consecutive admissions over a two year period to hospital facilities of the Phoenix Area of the Bureau of Indian Affairs. There were 256 Indian diabetic admissions, an over-all case-admission rate of 1.5 per cent for the entire area. The male case-admission rate was 1.4 per cent and the female case-admission rate was 1.6 per cent. The varying tribal prevalence was related superficially to possible differences in habitus, occupation and environment. Diabetic coma was not recorded in the presenting complaints of any of these patients or in their past histories, and the need for metabolic regulation was infrequent as a cause for admission. Obesity was common among diabetics admitted to the General Hospital of the Phoenix Area Medical Center, and in other respects the clinical characteristics of this disorder as observed in these patients were reminiscent of the "maturity-onset" type of diabetes described by others and correlated with relatively moderate deficiencies of plasma and pancreatic insulin. A definite increase in the prevalence of diabetes among hospital admissions of Indians with tuberculosis was noted. Tuberculosis among diabetic Indians was, almost without exception, of moderate to far advanced degree, and the increased severity of the diabetes, as compared with nontuberculous diabetics, seemed a reflection of the additive effects of infection. Conditions complicating diabetes were common and could be related to the known duration of the primary disorder. The prevalence of diabetes and its natural history as observed in this relatively homogeneous group of Indians of the American Southwest lend strong support to Joslin's thesis of the universality of this disease.

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CASE REPORTS

MACROCYTIC ANEMIA ASSOCIATED WITH INTESTINAL STRICTURES AND ANASTOMOSES: REPORT OF TWO CASES *

By Robert D. Pearson, M.D., *Scarsdale, N. Y.*

Evidence has accumulated that macrocytic anemia may be associated with intestinal strictures and anastomoses. That this condition is not widely known or recognized is demonstrated by the fact that only 61 cases have been reported thus far. Faber [1] in 1897 first reported a clinical picture of pernicious anemia associated with intestinal stricture. Other reports followed, and Little, Zerfas and Trusler [2] in 1929 reported the first case of macrocytic anemia associated with a short-circuiting intestinal anastomosis as distinct from stricture. Reviews of the subject by Meulengracht,[3] Barker and Hummel [4] and Cameron et al.[5] brought the total number of reported cases to 61. Intestinal anastomoses, primarily to circumvent strictures or diseased bowel, were the basic abnormality in 24 of these cases, while in 37 only strictures were present. Most of the strictures were in the small intestine but six were in the colon. Of the anastomoses, 15 were entero-enterostomies or enterocolostomies, and nine were gastrocolic or high jejunocolic fistulas.

Macrocytic anemia was first produced experimentally in animals by Seyderhelm et al.[6] in 1924. They formed fibrous strictures in the terminal ileum of dogs and sometimes could produce an anemia which closely resembled that of pernicious anemia in man. Jensenius [7] in 1945 found that removal of the distal two thirds of the small intestine in dogs caused a pellagrous state which was often associated with a macrocytic anemia. More recently, Cameron, Watson and Witts [8, 9, 10] produced 3 to 4 inch blind loops in the small intestines of rats and found that, if the loops were designed so as to be filled by peristalsis with intestinal contents, a macrocytic anemia developed in a high proportion of animals. Furthermore, liver extract, folic acid or Aureomycin instituted after the development of the anemia was effective in prolonging the duration of survival in the anemic rats as compared with the untreated controls. Similar procedures were carried out by Toon and Wangensteen,[11] who found that oral Aureomycin instituted prior to surgery would prevent the development of anemia in these operated rats. Watson and Witts [12] found, following construction of the intestinal blind loops, an alteration in the bacterial flora of the small intestine so that it resembled that ordinarily found in the cecum. These authors postulated that this alteration, presumably due to stagnation of the intestinal contents, might cause the anemia by leading to the loss of an organism which synthesizes hemopoietic material, or to the predominance of an organism which uses up hemopoietic

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material; or it is possible that a toxin is formed which in some way interferes with the synthesis, absorption or utilization of essential hemopoietic factors. Aureomycin presumably changes the intestinal bacteria in such a way that anemia is prevented.

The symptoms of intestinal macrocytic anemia associated with strictures and anastomoses may be indistinguishable from those of pernicious anemia. Glossitis is a frequent finding, and icterus is present in about half the cases. Involvement of the nervous system is frequently reported. The blood picture is usually identical with that of pernicious anemia, with hyperchromia, macrocytosis, poikilocytosis, anisocytosis and leukopenia. In the cases where the bone marrow has

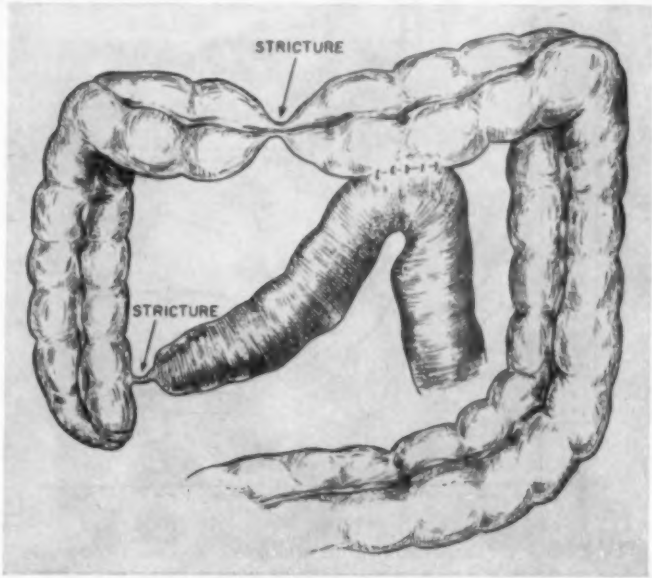

FIG. 1. *Case 1.* Drawing illustrating the ileotransverse colostomy short-circuiting the intestinal strictures. The ileum is markedly dilated both proximal and distal to the site of anastomosis.

been studied it is found to be hyperplastic and megaloblastic. In the 61 reported cases, steatorrhea was found in nine of the 10 cases in which the fat content of the stools was studied. It differs from pernicious anemia in that free hydrochloric acid has been found in over half the cases in which gastric analysis was performed, and it was possible to demonstrate intrinsic factor in the gastric juice in one case.[13] Furthermore, the anemia may be cured permanently by surgical correction of the intestinal abnormality. Liver therapy was used in 27 of the 61 reported cases; in five of these it was without effect, and in the remaining 22 cases a response of varying degree was obtained.

A report follows of two additional cases of macrocytic anemia associated with

intestinal strictures and anastomoses which have been studied at the Bronx Veterans Administration Hospital. These cases are of particular interest in that they show the response of this type of anemia to folic acid and vitamin B_{12}.

Case Reports

Case 1. A 30 year old white male was admitted to the hospital for the first time on February 14, 1947. In August, 1945, progressive, nontender enlargement of the right testicle had occurred. Orchiectomy was performed in October, 1945, and a diagnosis of seminoma was made. Excision of the right spermatic cord and several enlarged lymph nodes along the iliac vessels and the inferior vena cava was then performed, and was followed by extensive x-ray therapy to the pelvis, abdomen and

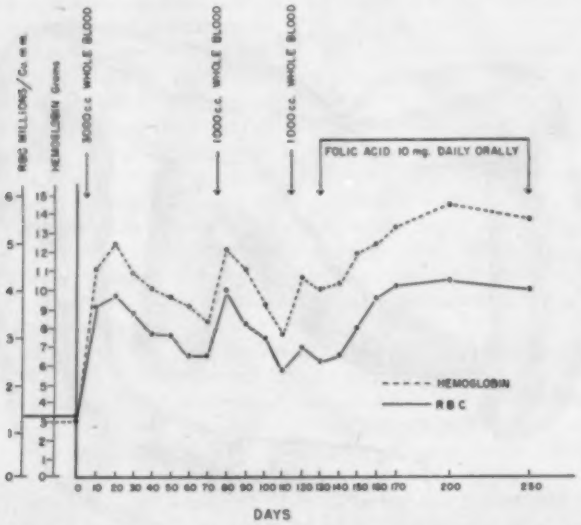

Fig. 2. *Case 1.* Graph showing the hemopoietic response to folic acid.

the mediastinum. Late radiation effect on the abdominal wall resulted in a draining sinus in the right groin for which the patient was admitted to the hospital.

After six months of supportive treatment the sinus healed spontaneously. In October, 1947, acute intestinal obstruction developed and 48 inches of gangrenous distal ileum were resected and an end-to-side ileocecostomy was performed. Shortly afterwards a fistula developed between the anastomotic site and the anterior abdominal wall. When the fistula was resected seven months later the anastomotic site was found to be stenotic, and the midtransverse colon was bound down and partially obstructed by dense adhesions. To circumvent these strictures a side-to-side anastomosis was made between the left side of the transverse colon and the ileum at a point about two feet proximal to the stenotic ileocecostomy site (figure 1). The patient was discharged from the hospital in July, 1949, at which time his red blood cell count was 4,400,000 and hemoglobin 14.9 gm. per 100 c.c.

For the next year and a half he remained at home doing well, and his weight rose from 102 to 118 pounds. Dietary intake was good, and bowel movements aver-

aged three to four light-colored stools daily. Six weeks before the second admission, on February 4, 1951, there was a progressive onset of weakness, exertional dyspnea, pallor and ankle edema. The tongue was not sore, and there were no distal paresthesias.

On the second admission the temperature was 102° F.; pulse rate, 130; respirations, 24; blood pressure, 100/40 mm. of Hg. The patient was pale and appeared both acutely and chronically ill. He weighed 118 pounds. The skin and sclerae were slightly icteric, and the eyegrounds showed fresh hemorrhages and exudates. The tongue and buccal mucosa were normal. There were a few scattered inspiratory râles at both lung bases and the heart sounds were of poor quality. The abdominal wall was leathery and indurated, and showed numerous operative scars. Peristalsis was hyperactive. The liver and spleen were not enlarged, and there were no abnormal masses or tenderness. The right testicle was absent. There was minimal

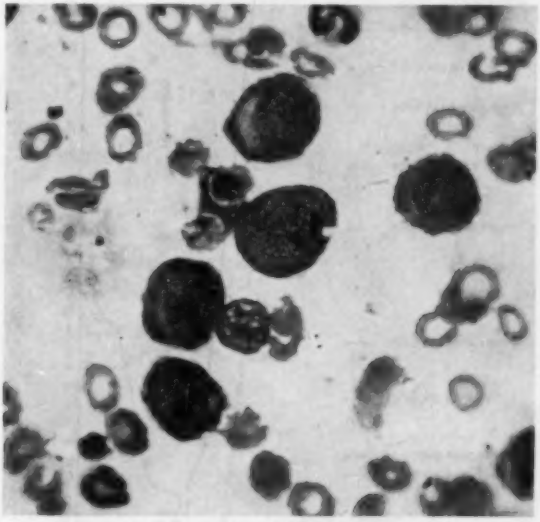

FIG. 3. *Case 1.* Sternal marrow smear before treatment, showing megaloblastic erythropoiesis. Wright's stain. × 900.

edema of both ankles and early clubbing of the nail beds. Neurologic examination was not remarkable except for the residua of a left peripheral facial paralysis. Rectal examination was negative.

The blood count revealed 1,350,000 red blood cells, 3.0 gm. hemoglobin, and 3,350 white blood cells. The differential count showed 4 per cent nonsegmented neutrophils, 56 per cent segmented neutrophils, 27 per cent lymphocytes, 4 per cent monocytes, 5 per cent eosinophils, 2 per cent metamyelocytes, 2 per cent myelocytes and 1 normoblast per 100 white cells. A smear showed marked anisocytosis, slight poikilocytosis and a preponderance of macrocytes. Platelet count was 76,000. Sternal marrow aspiration revealed a hyperplastic marrow containing 18 per cent megaloblasts, 5 per cent erythroblasts, 4 per cent normoblasts, 3 per cent myeloblasts, 11 per cent myelocytes, 6 per cent metamyelocytes, 8 per cent nonsegmented neutrophils, 21 per cent segmented neutrophils, 9 per cent lymphocytes, 4 per cent mono-

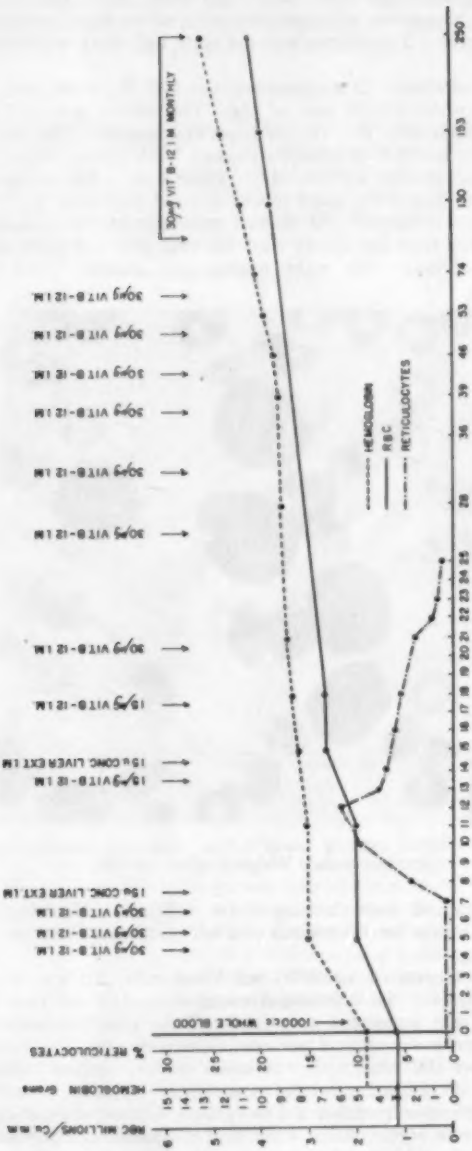

FIG. 4. *Case 1.* Graph showing the hemopoietic response to vitamin B_{12}.

cytes, 6 per cent eosinophils, 2 per cent reticuloendothelial cells, 3 per cent plasma cells. Urinalysis was negative. A VDRL microflocculation test for syphilis was negative. The blood urea nitrogen was 20 mg. per cent. The serum bilirubin was 2.0 mg. per cent, the alkaline phosphatase 2.1 Shinowara units, the cephalin flocculation 2 plus in 48 hours. The total serum protein was 6.0 gm. per cent, with 4.0 gm. per cent albumin and 2.0 gm. per cent globulin. The serum calcium was 11.2 mg. per cent. The stools were soft and light tan in color, and contained no occult blood. On a diet containing 51 gm. of fat, a 24 hour fecal fat study (per cent of dried feces) showed a total fat excretion of 41.7 per cent, a fatty acid excretion of 30.6 per cent and a neutral fat excretion of 11.1 per cent. A gastric analysis following histamine stimulation showed free hydrochloric acid up to 44 units. A glucose tolerance test using 100 gm. of glucose orally showed a normal curve.

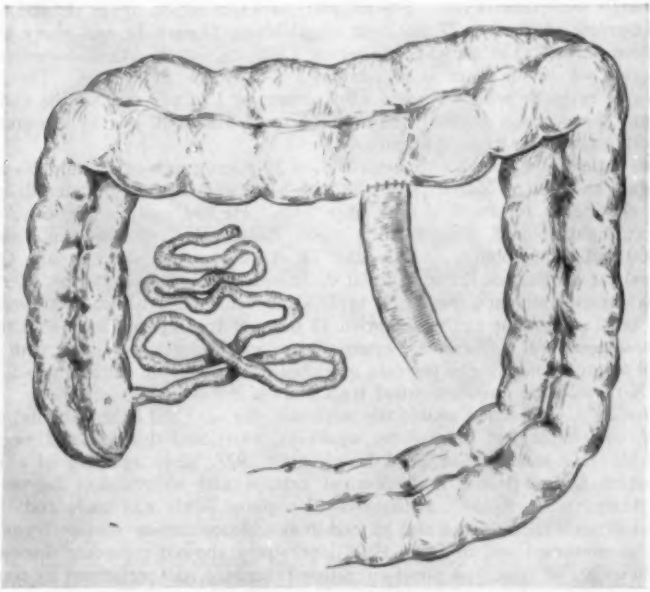

FIG. 5. *Case 2.* Drawing illustrating the ileotransverse colostomy and the markedly dilated transverse colon. The resected distal ileum which remains in situ forms a blind loop.

X-ray of the chest was negative. A bone survey showed no evidence of metastatic disease. X-rays of the gastrointestinal tract showed a patent anastomosis between the ileum and the transverse colon. The distal ileum and the ascending and proximal transverse colon filled with barium, although there was evidence of a stricture at the ileocecal junction and in the midtransverse colon. The ileum was markedly dilated both proximal and distal to the site of anastomosis with the transverse colon.

Multiple blood transfusions caused complete disappearance of megaloblasts from the marrow but were of only temporary value in raising the red cell count and hemoglobin. Gastroscopy showed normal stomach mucosa, with no evidence of a gastrocolic fistula. On June 21, 1951, the patient was discharged on an oral dose of 10 mg.

of folic acid daily, to be followed in the hematology clinic. A red blood cell count at that time was 2,500,000 and the hemoglobin was 10.2 gm. A smear still showed a preponderance of macrocytes. During the next two months there was a gradual rise in the red cell count to 4,200,000 and the hemoglobin to 14.5 gm. (figure 2). Since the patient was not under daily observation the reticulocyte response to folic acid could not be followed.

In October, 1951, folic acid was discontinued. With no specific therapy the hemoglobin averaged 12 gm. until June, 1952, when there was a rapid relapse in his blood picture, with a return of weakness, exertional dyspnea and ankle edema. He was re-admitted for the third time on July 18, 1952.

There was no essential change in the physical examination from that of the previous admission. The blood count revealed 1,210,000 red blood cells, 4.4 gm. hemoglobin and 5,350 white blood cells. The differential was normal, and most of the red cells were macrocytes. Sternal marrow examination again showed a hyperplastic marrow containing 27 per cent megaloblasts (figure 3) and many abnormal maturation forms. The patient was given 1,000 c.c. whole blood immediately and was started on 30 micrograms of vitamin B_{12} daily for three days. There was a reticulocyte response which reached a maximum of 11.2 per cent at the end of one week, and there was a gradual rise in the hemoglobin to 10 gm. by the end of two months of vitamin B_{12} therapy (figure 4).

The patient has since been maintained on 30 micrograms of vitamin B_{12} monthly. When last studied, in March, 1953, he had been working eight hours daily (as a private chauffeur) for the first time since 1945. He had continued to have three to four soft, light colored, foul smelling stools daily. His red blood cell count was 4,200,000 and hemoglobin was 13.2 gm. The bone marrow was normal. Quantitative fecal fat studies on 111 gm. of fat daily intake showed a total fat excretion of 62.7 per cent, a fatty acid excretion of 57.4 per cent and a neutral fat excretion of 5.3 per cent. A gastric analysis showed 43 units of free hydrochloric acid following an alcohol test meal. The total serum protein was 6.2 gm. per cent, with 4.5 gm. per cent albumin and 1.7 gm. per cent of globulin. The serum calcium was 9 mg. per cent. X-rays of the gastrointestinal tract showed no change.

Case 2. A 42 year old white male mechanic was admitted to the hospital on April 9, 1952, complaining of progressive weakness, exertional dyspnea and swelling of the ankles. He had been in good health until 1937, when episodes of alternating constipation and diarrhea, midabdominal cramps and weight loss began. While in the Army, in April, 1943, a diagnosis of regional ileitis was made and 18 inches of distal ileum were resected and an end-to-side ileocecostomy was performed. His symptoms continued and in June, 1948, laparotomy showed recurrent disease in the distal 36 inches of ileum. A short-circuiting procedure was performed by transecting the ileum 6 inches above the involved segment and anastomosing the proximal end to the transverse colon (figure 5). Six months later the patient was having three to four bowel movements daily, had gained 12 pounds of weight and was free of abdominal pain. X-ray examination at this time showed a patent anastomosis between the ileum and the transverse colon, and no evidence of disease in the small bowel. A red cell count was 3,900,000 and the hemoglobin was 13 gm.

From February, 1949, to November, 1951, the patient was able to work eight hours daily. He was asymptomatic except for occasional attacks of diarrhea. His dietary intake was excellent. Five months before admission there was progressive onset of weakness, exertional dyspnea and pallor. Two months before admission there were progressive swelling of the legs and paresthesias of the hands and feet.

On admission the temperature was 99° F.; pulse rate, 75; respirations, 20; blood pressure, 120/70 mm. of Hg. The patient was pale and appeared chronically ill. He weighed 136 pounds. There was no jaundice. The right fundus showed an area

of hemorrhage along the major inferotemporal vessel near the disc. The tongue and buccal mucosa were normal. The lungs were clear. There was a loud systolic murmur heard over the entire precordium. The abdominal wall showed numerous operative scars. The liver edge could be felt 3 cm. below the right costal margin on deep inspiration. There were no abnormal masses or tenderness. The left testicle was undescended. There was 2 plus edema of the lower extremities. There was no clubbing of the nail beds. No abnormal neurologic findings could be elicited. Rectal examination was negative.

The blood count revealed 800,000 red blood cells, 4.3 gm. hemoglobin and 2,400 white blood cells. The differential count was normal, but study of the red cells on smear revealed marked anisocytosis and poikilocytosis, and a preponderance of macrocytes. The mean corpuscular volume was 150 cubic microns, the mean corpuscular hemoglobin 53 micromicrograms, and the mean corpuscular hemoglobin concentration

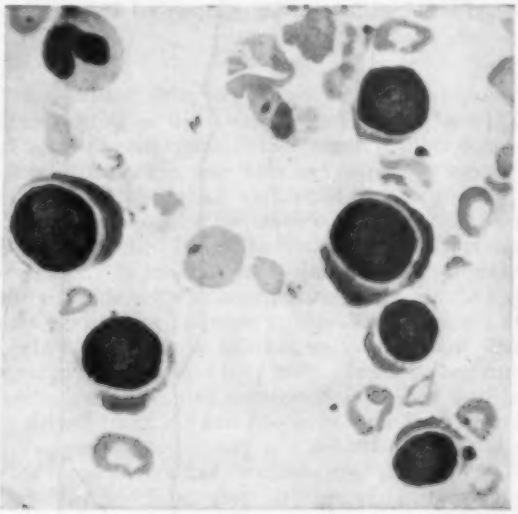

FIG. 6. *Case 2.* Sternal marrow smear before treatment, showing megaloblastic erythropoiesis. Wright's stain. × 900.

35 per cent. The urinalysis was negative. The serum calcium was 8.6 mg. per cent, the serum phosphorus 3.0 mg. per cent, and the total protein was 6.5 gm. per cent, with albumin 4.8 gm. per cent, and globulin 1.7 gm. per cent. Examination of the stools for occult blood was persistently negative, although they contained large amounts of neutral fats and fatty acids. No quantitative fecal fat studies were done. Sternal marrow aspiration revealed a hypercellular marrow containing 22 per cent megaloblasts (figure 6), 6 per cent erythroblasts, 25 per cent normoblasts, 4 per cent myelocytes, 10 per cent metamyelocytes, 11 per cent nonsegmented neutrophils, 10 per cent segmented neutrophils, 7 per cent lymphocytes, 1 per cent eosinophils, 2 per cent basophils, 0.5 per cent reticuloendothelial cells, 2 per cent plasma cells. A gastric analysis following histamine stimulation showed free hydrochloric acid up to 85 units.

X-ray of the chest was negative. X-rays of the gastrointestinal tract showed a patent anastomosis between the ileum and the transverse colon, and no evidence of

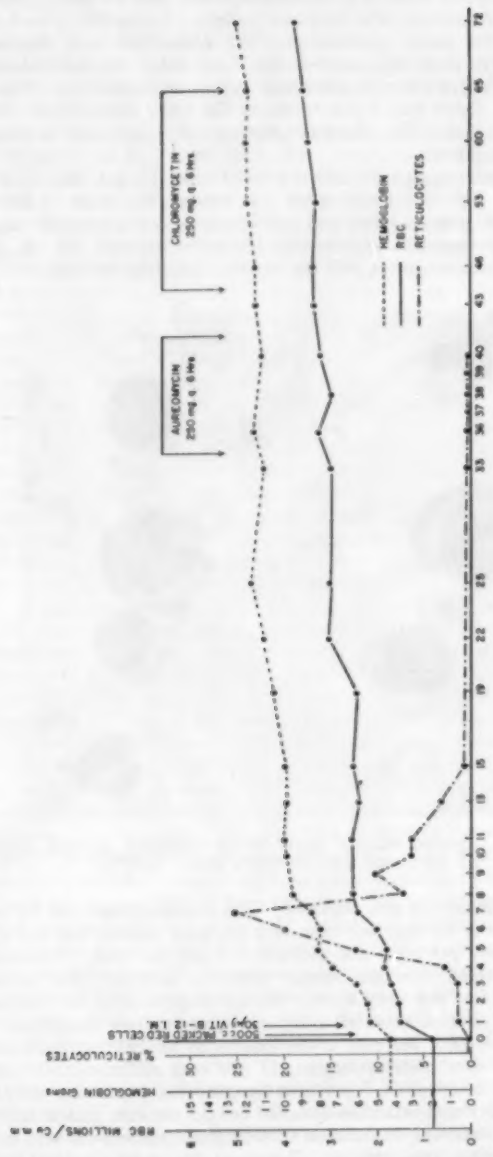

FIG. 7. *Case 2.* Graph showing the hemopoietic response to 30 micrograms of vitamin B_{12}.

disease in the small bowel. The large bowel was rather markedly distended. The distal ileum could not be visualized.

The patient was treated with 500 c.c. of packed red cells and 30 micrograms of vitamin B_{12} intramuscularly. At the end of one week there was a maximal reticulocyte response to 25 per cent, and the bone marrow showed only 1 per cent megaloblasts, but a marked normoblastosis of 57 per cent. At the end of one month the red blood cell count had risen to 3,000,000 and the hemoglobin to 11 gm. At this time the patient was started on 250 mg. of Aureomycin every six hours, but this was discontinued at the end of one week because of gastrointestinal irritation. There was no reticulocyte response to this medication. Chloromycetin was then given in doses of 500 mg. every six hours for three weeks and then discontinued. The blood count continued to improve so that, at the time of discharge on June 20, 1952, the red cell count was 3,700,000 and the hemoglobin was 12.5 gm. (figure 7). While in the hospital the patient had had three to five semi-solid, light tan stools daily. Following discharge he did not return to the hospital for follow-up.

Comment

In both of these patients there was little doubt that the anemia was related to the abnormalities existing in the intestinal tract. The clinical picture and the laboratory findings were quite typical of those found in other patients with macrocytic anemia of intestinal origin, and there was nothing to suggest the fortuitous association of other conditions which could cause such an anemia.

In view of the lack of recorded information concerning the effect of folic acid and vitamin B_{12} in this entity, it was interesting to note the response of our patients to these agents. In the first case folic acid and parenteral vitamin B_{12} produced an effective although a submaximal response. In the second case there was an excellent hematologic response to only 30 micrograms of vitamin B_{12}, but since the patient could not be followed we do not know what the ultimate maximal response to this drug may have been. In the second case, Aureomycin and Chloromycetin were both used during the time when there was a progressive rise in the red cell count and hemoglobin as a result of vitamin B_{12} therapy. Consequently, it is impossible to make any deductions as to the effect of these antibiotics on the blood picture had they been used alone.

The mechanism by which intestinal stricture or anastomosis gives rise to a macrocytic anemia is unknown. In both cases presented in this report several feet of small intestine had either been resected or short-circuited, and it is possible that the anemia was caused by inadequate absorption of hemopoietic substance. However, Jackson and Linder,[14] in a recent review of the literature concerning the effects of massive small intestinal resections, found that, on the whole, anemia is not a feature of intestinal resection. In all the reported cases of intestinal macrocytic anemia the fundamental abnormality could well be stagnation of the intestinal contents such as is seen in rats with intestinal culs-de-sac. For this reason Watson and Witts [12] postulate that in these cases change in the bacterial flora of the small intestine occurs so that there is interference with the formation or utilization of hemopoietic material. Recent evidence [15, 16, 17] supports this assumption.

Summary

Two cases are reported of macrocytic anemia, associated in one case with an ileotransverse colostomy to short-circuit intestinal strictures, and in the other

with resection of the ileum and ileotransverse colostomy to short-circuit an area of regional ileitis. The hematologic response of these cases to folic acid and vitamin B_{12} is shown.

ACKNOWLEDGMENT

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ACANTHOCHEILONEMA PERSTANS—THE PERSISTENT FILARIA: WITH A REPORT OF SIX CASES*

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BETWEEN June, 1952, and June, 1953, six patients who had been living in African missions were seen at the Cleveland Clinic with a diagnosis of infestation with *Acanthocheilonema perstans*. This report summarizes the six cases and emphasizes the importance of blood examination of persons who have been in endemic areas, especially if eosinophilia is present.

CASE REPORTS

Case 1. A 44 year old woman, a missionary, was first seen on June 5, 1952. She had spent 12 years in the Belgian Congo and had always been in excellent health. There were no symptoms of filariasis such as lymphangitis, lymphadenitis, fever, filarial abscesses or chyluria. The physical examination was normal. Blood smears showed many microfilariae of *A. perstans*. The stool examination was negative. The red blood cell count was 5,280,000, and the hemoglobin content 13.5 gm. The white blood cell count was 6,800, with 73 per cent neutrophils and *6 per cent eosinophils*. Smears for malaria were negative. The patient was treated with Hetrazan, 5 mg. three times a day after meals for 10 days. On July 16, blood smear showed a decreased number of microfilariae. On April 20, 1953, microfilariae were found in very small numbers by concentration technic. The diagnosis was confirmed by the Chamblee, Georgia, United States Public Health Service Station.

Case 2. A 32 year old man, a minister from Nigeria, was first seen on January 7, 1953. He had lived in Africa for three years. He had had malaria and typhus fever and had been infested with *Schistosoma mansoni*. He was asymptomatic. His red blood cell count was 5,300,000; hemoglobin content, 84 per cent; white blood cell count, 9,500, with *11 per cent eosinophils*. The blood smear revealed *A. perstans* microfilariae; and stools, *S. mansoni*.

The patient was given Hetrazan. At examination on February 13, 1953, many microfilariae were still present in peripheral blood.

Case 3. A 34 year old woman, who had been a missionary in Nigeria for three years, was first seen in April, 1950. The physical examination at that time was normal. In January, 1952, microfilariae were found in her blood. The hemoglobin content was 11.8 gm.; white blood cell count, 4,550, with *47 per cent eosinophils*. In September, 1952, *A. perstans* microfilariae were found.

On September 10, 1952, a 10 day treatment with Hetrazan was begun. Microfilariae were still present when the blood smear was rechecked on October 8, 1952.

Case 4. A 30 year old man, a minister, was admitted for a routine examination on June 18, 1953. He had been in Nigeria, West Africa, for four years. He had returned to the United States in June, 1953.

The physical examination showed him to be in excellent health. The white blood cell count was 17,150, with 22 per cent neutrophils, *54 per cent eosinophils*, 2 per cent monocytes and 1 per cent basophils. The hemoglobin content was 94 per cent. Blood smears showed *A. perstans* microfilariae, and the stool examination revealed *Endamoeba histolytica*.

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Case 5. A 30 year old woman, the wife of case 4, was also from the mission in Nigeria, West Africa. She had been in Nigeria for six years. This patient was seen on June 19, 1953, with no complaints. The physical findings were normal. The white blood cell count was 6,750, with *29 per cent eosinophils,* 25 per cent lymphocytes. The blood smear showed *A. perstans* microfilariae.

Case 6. A six and one-half year old child, the daughter of cases 4 and 5, had spent her entire life in Nigeria with the exception of one year, 1949. The physical examination was normal and she was asymptomatic. The white blood cell count was 16,850, with *42 per cent eosinophils.* The red blood cell count was 4,610,000. A blood smear showed *A. perstans* microfilariae.

A five year old boy, the son of cases 4 and 5, had a white blood cell count of 11,750, with *26 per cent eosinophils.* One blood smear was negative for *A. perstans* microfilariae, but the child may well have had the infestation.

Discussion

Geographical Distribution: A. perstans has an extensive distribution in tropical Africa (Sierra Leone, Gold Coast, Nigeria, Congo Basin, Uganda, Northern Rhodesia, Algiers and Tunis). The parasite is also widely distributed in coastal South America from Venezuela to Argentina, Panama, Trinidad, Dutch and British Guianas, and Brazil.[2, 3]

Incidence: The infection rate in northern Argentina varies from 39 to 51 per cent. In some areas of Africa such as Uganda, 90 per cent of the population is infested.[4] Stoll (1947) has estimated the world incidence of the infection at 27,000,000 cases, consisting of 19,000,000 in Africa and 8,000,000 in tropical America.[2, 3] In the Belgian Congo there is 60 per cent infestation in river villages.[6] Europeans are less susceptible than natives. In Africa *A. perstans* is often associated with Bancroft's filaria and *Loa loa,* and in South America with *Mansonella ozzardi.*[2]

Morphology, Biology and Life Cycle of the Parasite: The adult worms of the genus live in the body cavities. They are most common in the peritoneal cavity and least common in the pericardium.[2] They live in the mesentery [3] and in the retroperitoneal tissues, and may become walled off in cysts in the large body cavities.[7]

The adults are creamy white, elongated, cylindroid filariae, with a smooth cuticula, bluntly rounded unarmed anterior end surmounted by a shield having a pair of large lateral and two pairs of submedian papillae, and a caudal extremity curved ventrad in both sexes and bifurcated, forming a pair of triangular non-muscular flaps. The male measures about 45 mm. by 60 microns; the female, 70 to 80 mm. by 120 microns. The posterior end of the male is distinguished by having one postanal and four preanal pairs of papillae and very unequal rodlike copulatory spicules. The microfilariae are not strictly periodic, but their numbers in peripheral blood are fewer during the day than during the night.[2, 3]

The microfilariae measure 200 by 4.5 microns, are unsheathed, and are capable of considerable extension and contraction.[2] The detection and identification of the unsheathed microfilariae of *A. perstans* in the peripheral blood are diagnostic. They may be differentiated from the microfilariae of *M. ozzardi* by the position of the caudal nuclei; in *A. perstans,* the caudal nuclei extend into the posterior tip of the blunt tail, but in *M. ozzardi* they do not [4] (figure 1).

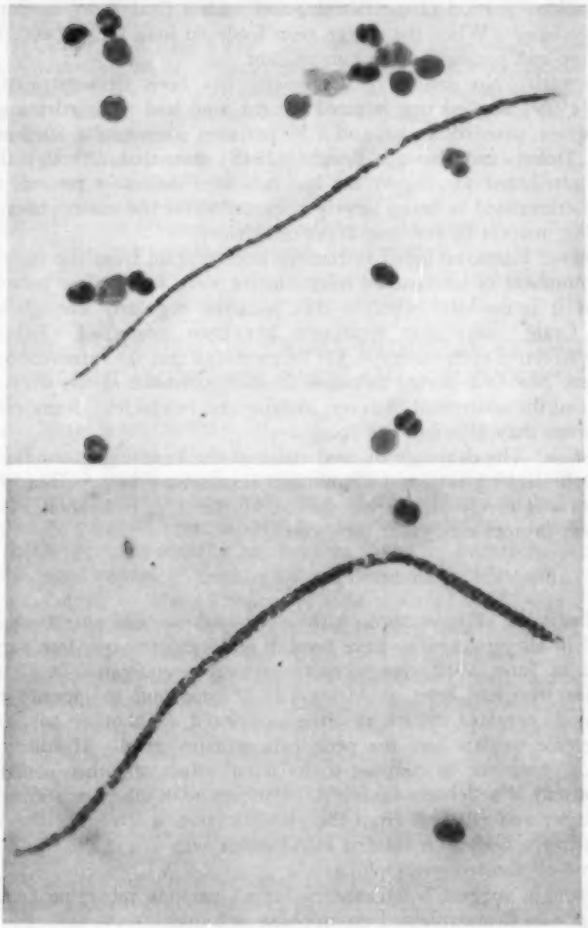

FIG. 1. Unsheathed microfilaria of *A. perstans* in thick blood film (hematoxylin stained). Note caudal nuclei extending to tip of blunt tail and other morphologic characteristics. (Case 1, above; case 2, below.)

In Africa the intermediate hosts of *A. perstans* are species of *Culicoides* (*austeni* and *grahami*).[2] These midges bite only in the dark,[7] and some people therefore sleep with the lights on. The microfilariae are ingested with the blood of the host by the bloodsucking midge in whose body they undergo metamorphosis. The successive stages of development in *C. austeni* are unknown.[8] Seven to 10 days after the midge bites the definitive host, the mature infective larva, 600 to 1,000 microns, wiggles down the proboscis of the midge, ruptures

the membranous portion of the labrum, and with a final jerky motion emerges upon the surface.[1] When the midge next feeds on man the parasite leaves the vector midge and penetrates the human skin.

Pathogenesis: No definite pathogenicity has been demonstrated in man. Morenas (1929) studied one infected patient who had toxic edema of the left eyelid, dyspnea, precordial pain and a 50 per cent eosinophilia attributed to the infection. Dubois and Van den Berghe (1948) state that, although the allergic dermatitis attributed to *A. perstans* has not been definitely proved, the filaria has been incriminated as being largely responsible for the eosinophilia so widely found among natives in endemic areas of Africa.[2]

Treatment: Hetrazan failed to remove microfilariae from the blood. Sometimes the numbers of unsheathed microfilariae were fewer after treatment than before, but it is doubtful whether this occurred regularly enough to be significant.[5] Craig [2] says that treatment has been unstudied. Belding [1] says there is no effective chemotherapy, yet he mentions that the intravenous injection of methylene blue is reported to cause the disappearance of the microfilariae in the blood and the abatement of fever, malaise and headache. Removal from the endemic areas may alleviate the condition.

Prevention: The drainage of land reduced the breeding grounds of midges. Use of mesh sleeping nets and illuminated homes may help.[1] The females are night biters and rarely attack man before 10 p.m. A full moon, electric light or wind will protect man from their bites.[1]

Summary

The diagnosis of infestation with *Acanthocheilonema perstans* should be considered in all persons who have been in endemic areas. After our first case was found in June, 1952, five more cases were encountered in 12 months in missionaries who had been in Africa. It is important to identify the microfilariae as *A. perstans,* which is often associated with other parasites. It is not pathogenic to date and the prognosis remains good. Hetrazan has little effect on *A. perstans,* in contrast to its lethal effect on other nematodes such as *Loa loa* and *Wuchereria bancrofti.* Patients with acanthocheilonemiasis are asymptomatic, and removal from the endemic area will reduce the number of organisms in the body. A routine blood smear was diagnostic in all six of our patients and all showed eosinophilia.

We strongly suggest blood smears for all persons returning from endemic areas, especially if unexplained eosinophilia is found.

Acknowledgment

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FACTITIAL THYROTOXIC CRISIS INDUCED BY DEXTRO-AMPHETAMINE SULFATE AND THYROID *

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NUMEROUS case reports have appeared concerning induced states of thyrotoxicosis through self-administered overdoses of thyroid medication.[1, 2, 3, 4] The use of thyroid to simulate heart disease has been reported.[5, 6] The use of amphetamine to the point of toxicity has been reported on numerous occasions.[7, 8] There is one listed report of the use of amphetamine to the point of causing thyrotoxicosis factitia.[9] The following case is reported to illustrate the self-administered use of thyroid and amphetamine to such excess that not only was thyrotoxicosis simulated, but also the actual clinical diagnosis of acute thyrotoxic crisis was seriously considered. This might have been accepted except for certain suspicious factors in the past medical history and the laboratory data.

CASE REPORT

In July, 1950, a 47 year old white unmarried practical nurse was received in transfer at Jefferson Hospital with the complaints of nervousness, loss of weight, fever and sweats, shakes, muscular pains, abdominal cramps, generalized weakness, nausea and dryness of the mouth.

History of the present illness revealed that the patient had been intermittently ill since childhood with frequent episodes of fatigue, headache, joint pains, sore throats and marked difficulty in eating and sleeping. In 1920 the patient had had a complete thyroidectomy; the exact pathologic and clinical reasons for this could not be determined. Convalescence was poor, with frequent headaches, rapid heart beat, shortness of breath and weakness. These symptoms were not completely incapacitating, but they persisted; and between 1930 and 1934, for some uncertain reason or illness, she was a complete bed patient. In 1940 the patient took up practical nursing and worked for 18 months in a tuberculosis sanatorium. From 1943 until admission her presenting complaints became progressively worse.

In 1945 the patient was studied in a large teaching hospital and diagnoses of paroxysmal auricular tachycardia, anxiety hysteria and "increased tolerance to

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From the Department of Medicine, Jefferson Medical College Hospital, Philadelphia.

opiates" were made. Addiction was evidently not conclusively proved. In 1948 the patient became ill with "pneumonia." There were blood streaked sputa, but repeated examinations failed to reveal any acid-fast organisms, and repeated chest x-rays were normal. In 1948 she was hospitalized for dysuria and hematuria. No additional information could be elicited about this.

In June, 1950, the patient was admitted to another hospital for the presenting complaints. Physical examination reportedly revealed fine hand and tongue tremor, thyroidectomy scar but no palpable thyroid gland, tachycardia of 136, marked emaciation and questionable exophthalmos. Complete blood count, urinalysis, serum calcium, nonprotein nitrogen and cholesterol were normal. Basal metabolic rate was plus 45 and plus 63. Glucose tolerance curve was (mg. per cent): fasting, 80; 30 minutes, 170; one hour, 235; two hours, 215. Kidney, ureter and bladder film was normal. Chest x-ray showed flattening of diaphragm leaves only. Electrocardiogram revealed a sinus tachycardia. A diagnosis of thyrotoxic crisis was made, and the patient was digitalized and then received digitoxin, 0.2 mg. daily, and propylthiouracil, 100 mg. every six hours for two days, then 160 mg. every six hours. After two days her temperature was 104° F., pulse was 150, and the patient "appeared to be in the throes of thyrotoxic crisis." She was then transferred to Jefferson Hospital. In the notes of her referring physician was the following comment: ". . . Over the past 30 years she has had many diagnoses. Her life has been threatened many times with episodes which appear like thyroid crisis. It is believed she is suffering from thyrotoxicosis despite her lack of response to thyroid depressing agents and the absence of palpable thyroid."

On admission to Jefferson the patient added to her history that she had lost 15 pounds in six months, had had anorexia for three months, and on occasions suffered from precordial, cramplike pain with radiation to the right arm, often lasting as long as one-half to one hour.

Past medical history revealed the usual childhood diseases, no other serious medical illnesses except as mentioned, and no definite history suggestive of rheumatic heart disease. Surgical history included tonsillectomy as a child, thyroidectomy at the age of 17 years, and a uterine dilatation and curettage at the age of 15 years, all for unknown reasons.

Family history was noncontributory. Personal history at this time revealed no further pertinent information.

Physical examination at the time of admission revealed: temperature, 100° F.; pulse, 136; respirations, 44; blood pressure, 136/82 mm. of Hg. The patient appeared older than 47 years; she was thin, poorly nourished and developed, and her voice was weak and hardly perceptible. She was orthopneic in an oxygen tent. There was no cyanosis, but neck veins were slightly distended. Skull and scalp were normal, conjunctivae were pale but the eyes were otherwise normal, as were the nose, ears, mouth and oral pharynx. The neck revealed a low transverse (thyroidectomy) scar, with no palpable thyroid gland or other masses. Thoracic cage was normal. Breasts were atrophic but otherwise normal. Examination of the lungs revealed slight generalized increase in bronchovesicular breath sounds, thought to be due to the patient's emaciation. Except for a rapid, questionably irregular rate of 136, the heart was normal. There was no response to carotid sinus pressure. Abdominal, genital, pelvic and rectal examinations were normal. The extremities showed marked but symmetrical loss of muscle bulk. Reflexes were normal.

Studies revealed: hemoglobin, 11 gm. or 71 per cent; red blood cells, 3,660,000; white blood cells, 19,600, with 91 per cent segmented neutrophils, 4 per cent nonsegmented neutrophils and 5 per cent lymphocytes. Subsequently the white cell counts and differentials were normal. Urinalysis revealed a faint trace of albumin, which was subsequently negative. Wassermann and Kahn tests were negative. In milli-

grams per cent the nonprotein was 35; blood urea nitrogen, 15; non-fasting blood sugar, 100; * serum cholesterol, 225; * calcium, 9.5; phosphorus, 3.6; plasma chlorides, 572; bilirubin, 0.6. Total proteins were 7.89 gm. per cent (albumin/globulin ratio, 5.29/2.6); alkaline phosphatase, 4.72 units; urea clearance, 72 per cent; erythrocyte sedimentation rate was normal. Circulation time was 10 seconds (arm-to-tongue Decholin). Gastric washings, smear and culture were twice negative for acid-fast bacilli. PPD No. 1 was slightly positive; skull x-rays were normal, and chest x-ray (twice repeated) was normal. Twenty-four hour urine for 17-ketosteroids revealed 4.0 mg. equivalents of androsterone per 24 hours. Repeat 12 hour specimen revealed 2.24 mg. I_{131} uptake (150 millicurie dose) was 1 per cent, and repeated six weeks later was 4 per cent. Protein bound iodine determinations were not done at this institution at the time of this patient's hospitalization. Electrocardiogram at admission revealed a well controlled auricular fibrillation with a ventricular rate of 130. A subsequent electrocardiogram was normal (after cessation of patient-administered medication). The consulting cardiologist's opinion was paroxysmal auricular fibrillation of undetermined cause, not due to thyrotoxicosis. The use of digitalis and quinidine was recommended. Basal metabolic rate under sedation, after cessation of self medication, was plus 2.* The consulting endocrinologist did not believe the patient to be thyrotoxic and considered miliary tuberculosis as one possible diagnosis.

Progress: The patient remained unchanged for several days. The past history of many episodes resembling thyrotoxic crisis with almost miraculous recovery, the failure to respond to antithyroid drugs, the lack of clinical findings to correspond to the systemic toxicity, the relatively normal laboratory studies (relative to thyrotoxicosis) alerted suspicion toward patient-induced disease. While she was at the x-ray department her belongings were searched, and thyroid extract and Dexedrine tablets were found hidden in a suitcase. Interrogated, the patient admitted taking these in substantial amounts. The exact amount could not be ascertained. Removal of the drugs resulted in cessation of symptoms and uneventful recovery. The psychiatric consultant was of the opinion (after numerous interviews) that the patient represented a mixed reaction of anorexia nervosa, acute anxiety state, guilt complex and hysteria. Uncovered was the occurrence of obesity in the patient's family, antagonism to her mother, frustration in her teaching studies into which she was forced, secondary gain of sympathy and favor during illness from early childhood, and an almost complete absence of contacts, friends, hobbies and interests. The patient had very little insight (to the point of asserting she thought the Dexedrine and thyroid were candy mints). The psychiatrist held out little hope that psychotherapy would help the patient. He considered suicide a definite risk if the patient were to gain insight. Because of her abuse of the drug, the patient was discharged to her family physician without thyroid medication for her true state, that of hypothyroidism.

A report from the patient's referring physician in July, 1953, after an interval of almost three years, revealed the following positive findings: pulse, 128; weight, 94½ pounds; fine tremor of tongue and upper extremities. There was no history of further episodes resembling thyrotoxicosis, and no history of further thyroid or Dexedrine medication. In her physician's opinion, she appeared to be in better health than he had ever observed previously.

Summary

Thyrotoxic crisis with typical antecedent history and distinctive findings offers little in the way of diagnostic difficulties. This case is reported to illustrate how

* Varying from report of previous hospitalization.

the acute findings of thyrotoxic storm may be simulated by the combined use of thyroid and amphetamine in adequate amounts. Lack of correlation of past history and of laboratory findings with the clinical manifestations of thyrotoxic crisis should arouse suspicion of patient-induced disease.

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PNEUMATOSIS CYSTOIDES INTESTINALIS: REPORT OF A CASE *

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PNEUMATOSIS cystoides intestinalis (pneumatosis cystoides intestorum hominis, gas cyst of intestine, pneumatosis cystoides intestini) is an uncommon condition characterized by multiple gas-containing cysts found in various portions of the gastrointestinal tract. The case described extensively by Bang [1, 2, 3] in 1876 is usually quoted as the first authentic case. Finney,[2] in 1908, was the first to report a case in the American literature. Mills [3] gave an extensive review of the subject, with three of his own cases bringing the total to 100 reported cases in 1925. In 1940 Jackson [4] reported one case of his own, and cited 172 cases reported in the world literature. A review by Koss [5] in 1952

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From the Medical Service, Fitzsimons Army Hospital, Denver, Colorado.

revealed 213 published cases. This entity has seldom, even today, been diagnosed before operation or autopsy.

In his review in 1925 Mills made the following remarks: "The condition has never so far been diagnosed previous to operation: the x-ray may be expected to wipe out this reproach." The reproach has not been wiped out, probably because this disease is seldom described in the standard textbooks of medicine. We believe that, as knowledge of the disease becomes more widespread, the

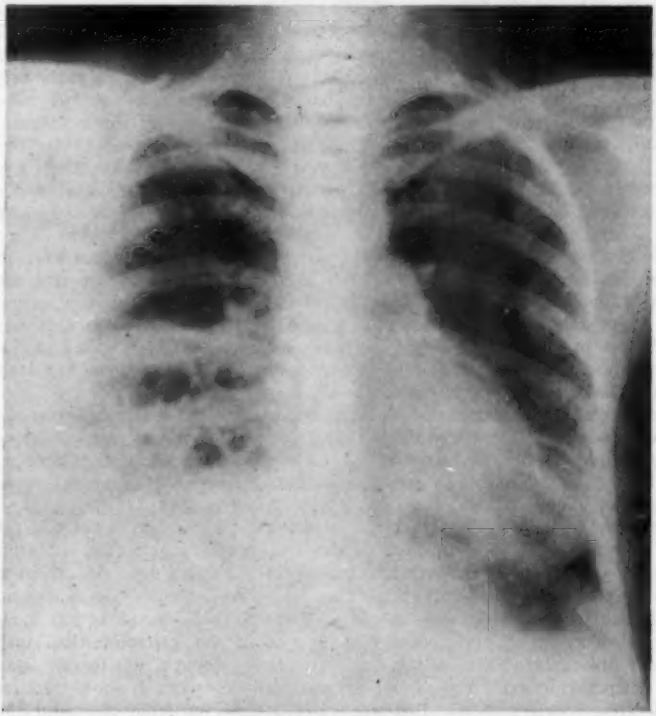

FIG. 1. Posterior anterior chest roentgenogram showing multiple cystic areas interposed between the liver and the right leaf of the diaphragm.

diagnosis can be made previous to operation, permitting better management of such cases.

CASE REPORT

A 37 year old white housewife was admitted to Fitzsimons Army Hospital on February 15, 1944, with a history of epigastric gnawing pain accompanied by excessive belching. This pain would come on approximately two hours after meals and was relieved by the intake of warm milk or sodium bicarbonate. The pain would occur daily in episodes lasting several weeks, and then would disappear and not recur

for several months. A diagnosis of duodenal ulcer had been confirmed in December, 1942, by gastrointestinal roentgenography. The patient had received partial relief by bland diet and antispasmodic medication. Her chief complaint at this admission was abdominal distention of approximately five weeks' duration. With the gradually increasing abdominal distention there was progressive diminution of epigastric distress. The patient had induced vomiting on several occasions in an effort to relieve the bloating sensation which had accompanied the distention. The remainder of the past history and family history did not appear significant.

The physical examination at time of admission revealed a temperature of 98.8° F. orally, pulse 84, and blood pressure 104/86 mm. of Hg. The patient appeared chronically ill, with moderate weight loss, but did not appear acutely ill. There was diffuse abdominal distention, with a tympanitic percussion note over the entire abdomen obliterating the usual area of liver dullness. There were no palpable organs or masses. Peristaltic sounds were heard but no visible peristalsis was noted. No direct or rebound tenderness was present. The remainder of the examination was essentially normal. Admission hemogram revealed red cells of 4,600,000; hemoglobin, 13.2 gm.; white blood cells, 6,800, with 72 per cent neutrophils, 20 per cent lymphocytes, 6 per cent monocytes and 2 per cent eosinophils. Urinalysis was normal. Kahn test was negative. Chest roentgenogram of February 15 showed clear lung fields. There was marked elevation of both leaves of the diaphragm. There were multiple cystic areas interpreted as loops of small bowel interposed between the liver and the diaphragm on the right (figure 1). There appeared to be free air under the diaphragm on the left. Roentgenograms of the abdomen with the patient in the dorsal, right and left lateral decubitus position were interpreted as showing air in several loops of small bowel and in the colon, indicating an ileus with a slight degree of obstruction in the lower bowel. These findings were felt to be consistent with the diagnosis of a ruptured viscus.

Because of the evidence of free air in the abdomen, a history suggesting partial obstruction and a substantiated diagnosis of previous duodenal ulcer, it was decided that the situation warranted exploratory laparotomy. The clinical picture was confused by the fact that the patient had a normal temperature, normal white blood count and no abdominal tenderness.

On February 16 a high right rectus incision was made. When the peritoneal cavity was opened free air escaped. The ileum contained numerous subserosal, gas-filled cysts of varying sizes, over its antimesenteric surface for a length of approximately four feet near its terminal portion. The involved ileum was distended and no evidence of peristalsis was noted. There was believed to be no evidence of pyloric obstruction or perforation in any area of the gastrointestinal tract. Accordingly, the involved area of the ileum was resected and a side-to-side anastomosis of the ileum performed. The patient left the operating room in good condition. The postoperative course indicated that she was not suffering from gastrointestinal tract obstruction in that she had normal bowel movements, passed flatus and was not distended.

On March 5, three weeks postoperatively, the patient had a sudden onset of severe epigastric pain. A roentgenogram of the abdomen revealed free air under the diaphragm. At laparotomy a perforated duodenal ulcer was found. There was no evidence of intestinal pneumatosis visualized at this operation. Following the closure of the perforated duodenal ulcer the patient showed persistent gastric retention. On April 10 a posterior gastroenterostomy was performed. There was no evidence of recurrence of the pneumatosis of the intestine. The patient was last seen in the Gastrointestinal Clinic on January 10, 1953. At that time she stated she had epigastric pain coming on two or three hours after meals, relieved by food, milk and antacids, no hematemesis or melena. Roentgenograms of the upper gastrointestinal

tract revealed a possible marginal ulcer. She is being followed in the Clinic in this respect.

The gross specimen (figure 2) consisted of 85 cm. of small intestine. There was a considerable portion of the mesentery attached which showed no abnormality. Over approximately one-half of the serosal surface, opposite the mesenteric attach-

FIG. 2. The gross specimen resected at the time of surgery.

ment, numerous gas-filled cystic areas were present, measuring from a pinpoint to several centimeters in size. The cyst walls were transparent. Grossly, the mucosal surface appeared normal.

The mucosa was intact, with no cysts noted. The submucosa and muscularis contained a few eosinophils, round cells and polymorphonuclear cells. The serosa contained numerous cystic areas which were empty except for occasional small

FIG. 3. Photomicrograph showing the multiple cystic areas in the subserosa. Note the absence of cystic areas in the mucosa.

amounts of serous material (figure 3). In some areas the cysts were lined with flat, serosa-like cells (figure 4). In other areas no lining cells were apparent, the lining being of a fibrous tissue. In some areas cysts were adjacent to blood vessels and contained a flat cellular lining suggesting lymphatics. The larger cysts did not bear any noticeable relation to vessels, and the lining, when present, suggested serosa type cells. There was a definite inflammatory cellular infiltrate in the serosal area in relation to the cysts, consisting of round mononuclear cells, polymorphonuclear cells and occasional eosinophils. No giant cells were noted in any of the microscopic sections.

ETIOLOGY

Five theories of etiology have been mentioned, namely, neoplastic, bacterial, chemical, mechanical and dietary deficiency. Bang believed the gas was produced by neoplastic cells. In the original American case Finney, along with Dr. William Welch, believed this represented a neoplastic growth with a type

of cell that produced gas. This concept is not given serious consideration today, as neoplastic cells cannot be identified on microscopic study.

Some of the earliest writers believed the gas was formed by gas-forming microörganisms. The cysts are sterile in the majority of cases and the flora highly variable in other cases. Spontaneous pneumoperitoneum has been frequently reported, but peritonitis accompanying the pneumoperitoneum has not been reported and this is believed to mitigate against the bacterial origin of the

FIG. 4. Photomicrograph from the wall of one of the cysts demonstrating the flat serosal type lining and inflammatory cells in the cyst wall. (× 300.)

disease. A more recent theory is that gases are formed in a chemical process related to altered metabolism of the cells.[5] This theory might be associated with the theory of dietary deficiency to be mentioned later.

The two most accepted theories as to the origin of the gas are (1) that it is mechanical, and (2) that it is due to dietary deficiency. The mechanical theory, the one accepted by most authors, propounds that the gas is forced into lymphatic channels distending lymphatic spaces. In a series of experiments using five dogs, Tung and Ngai [6] outlined the lymphatics of the intestine with a fatty meal or indigo ink and then found the air injected into the intestinal wall musculature followed these outlined channels. The air disappeared within a period of 48 hours following injection. The same authors described a patient with mucosal ulceration and pyloric obstruction operated on under spinal anesthesia. Vomiting occurred while the abdomen was open, and a cyst on the bowel appeared to fill during the vomiting while the lumen of the bowel did not change size. A disturbing factor in the mechanical theory is the fact that the cysts are often some distance from the mucosal ulceration.

The second most acceptable theory is that pneumatosis is due to serious dietary deficiency. Eveleth and Biester [7] produced the lesion in 16 of 22 pigs by a deficiency diet consisting of polished rice and washed casein. When skim milk made up 50 per cent of the ration the lesions were prevented. Whole corn, unpolished rice and yeast also tended to prevent the development of cystic pneumatosis in pigs. They were unable to determine the exact deficiency that led to the disease. This theory is somewhat attractive in that a large number of the human patients with this disease have pronounced digestive disturbances secondary to associated diseases.

Pathology

The cysts are usually located in the small bowel, more commonly on the antimesenteric border of the serosa, but may be located in the large bowel or in both large and small bowel. Cysts have been reported in the stomach and in the mesentery. The cysts may be predominantly subserosal and vary greatly in size, or they may be predominantly mucosal, in which case they are small and more uniform in size, often being likened to soap bubbles or honeycomb. The cysts may be distributed in all layers of the bowel wall. The composition of the gas has not been satisfactorily settled. Microscopically the cysts are empty except for occasional small amounts of serous-like fluid. Descriptions of the cyst lining are not uniform and range from collagen tissue to epithelium. In most cases the cysts appeared to be at least partially lined with a flat serosa-like cell, resembling gas-filled lymph channels; this supports the more popular mechanical theory for development of the cysts. In association with the cyst there is an inflammatory and foreign-body type of reaction, with giant cells of the mononucleated type reported, as well as acute and chronic inflammatory cells with fibrosis.

Diagnosis

The majority of the cases are associated with two common factors, mucosal ulceration and obstruction of the alimentary canal. Fifty per cent of the 85 cases reported by Nitch [8] in 1923 were associated with ulcers of the duodenum

or stomach. Thirty-six of these, or 83 per cent, had partial or complete obstruction. Fifty-eight per cent of the cases reviewed by Koss were associated with pyloric obstruction and ulcerating lesions of the pyloric area, 55 per cent had gastric or duodenal ulcers, and in 3 per cent carcinomas of the stomach were found. Moore [9] reported four cases in infants, all of whom died of enteritis. He was unable to find bacteria in the cysts. Other diseases reported associated with pneumatosis include intestinal tuberculosis, chronic and acute appendicitis and many others, such as intestinal obstruction due to gall-stones, chronic colitis and intestinal parasites. When no associated lesion can be found, as was the case in 15 per cent of those reported by Koss, the disease has been called primary pneumatosis cystoides intestinalis and is usually in the ileocecal region.

Lerner and Gazin [10] stated: "The roentgenographic findings consist primarily of the presence of translucent areas lying within the contour of the normal bowel. When a contrast medium, such as barium, is used there is inability to completely fill out the lumen of the bowel, giving the impression of filling defects. The presence of inconstant filling defects of increased translucency is pathognomonic." There may also be spontaneous pneumothorax. Roentgenographic examination may also reveal interposition of cystlike lesions between the liver and the right leaf of the diaphragm when the cysts are present in the small bowel. This finding is clearly demonstrated in our case (figure 1).

Therapy

The disease has often been stated to be benign and self-limited; however, cases definitely leading to obstruction have been reported.[5, 10, 11, 12] In the case reported by Lerner and Gazin, symptoms of intestinal obstruction gradually subsided under conservative therapy. It was Jackson's opinion in 1940 that the condition is self-limited and eventually undergoes a fibrous tissue healing. It therefore requires no treatment per se when found coincident with gastrointestinal lesions at operation. It is our opinion that the treatment in this disease has to be devised according to its manifestation, especially when it is the primary cause of gastrointestinal tract obstruction in itself.

Summary

A case of pneumatosis cystoides intestinalis is reported. Fifty to 60 per cent of the cases are associated with ulcerating and obstructing lesions involving the pyloric area. Fifteen per cent of the cases are primary in that they are not associated with other lesions. The most accepted theory as to its development is the forcing of gas through intestinal ulceration into lymphatic channels. It seems likely that dietary deficiency plays a part in a certain number of cases. Cases with definite obstruction due to pneumatosis cystoides intestinalis leading to death have been reported.

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MASSIVE DYSTROPHIC CALCIFICATION OF THE MYOCARDIUM *

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Massive calcification in myocardial infarcts is relatively uncommon. Although there are not more than 21 undoubted cases in the medical literature to date, the condition occurs in a well defined group of patients with a characteristic clinical picture and may be demonstrated by standard radiologic technics. The diagnosis is of some prognostic import since these patients, like others with coronary heart disease, are prone to sudden death.

Dystrophic calcification is the term applied to the laying down of calcium in dead, degenerated or devitalized tissue, as in infarcts. This constitutes the most common type of pathologic calcification and is not associated with abnormalities of calcium or phosphorus metabolism per se.

This type of calcification can thus occur without changes in the circulating blood calcium content. Dystrophic calcification has been related to the low production of carbon dioxide and the slow metabolizing tissue which permits the development of a local zone of alkalinity and, consequently, reduction of calcium solubility.[1] This phenomenon becomes more marked and more extensive in the presence of metabolic upsets such as occur in an area of infarction.

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Another explanation may be as follows: In a saturated solution of a poorly soluble substance like calcium phosphate the relations of the concentration of ionic calcium and phosphate, molecular calcium phosphate and the undissolved salt, following the loss of ionic equilibrium, explain in some instances the laying down of calcium substances in an area of necrosis. The enzymatic degradation of tissues with their content of nucleotides, phospholipids and phosphoric acid esters results in an excess of phosphates which could easily cause calcium to be precipitated from its physiologic levels.[2]

On the contrary, metastatic calcification is associated with increased availability of calcium. This type of mineralization is thus found in bone destructive lesions, with hyperparathyroidism and hypervitaminosis D and with renal insufficiency.

In 1908 Simmonds[3] unexpectedly discovered a gross calcified myocardial infarct at autopsy. At present, approximately 21 cases have been reported in the literature. These include several which were found coincidentally at autopsy. Brean et al.[4] have compiled the largest series and the most comprehensive study of this condition. With one exception, all of the 21 patients reported in the literature were males. Brenner and Wachner[5] reported a calcified myocardial infarct in a 64 year old woman who had a history of classic acute infarction 10 years previously. Physiologic impairment as manifested by angina pectoris was present in nine of the 14 cases. Of these nine, three had mild angina pectoris. Eleven of the 14 patients had electrocardiograms which showed evidence of myocardial damage; eight of the 11 showed disturbance of rhythm or conduction; three had auricular fibrillation, two had paroxysmal ventricular tachycardia, and six had intraventricular block or bundle branch block. Two patients had significant S-T displacement, and one of these proved at autopsy to have a fresh myocardial infarct. The average age of the patients was 63 years: the eldest was 74 and the youngest 44. Many of the men in this series were able to do heavy manual work in spite of the myocardial lesion. Physiologic cardiovascular impairment, based upon this series, seems to be the exception rather than the rule insofar as clinical incapacitation is concerned. This would also hold true for the case herewith reported.

Among the 21 cases reported in the literature the shortest duration between infarction and the discovery of myocardial calcification was approximately six years.

The prognosis in this disease remains obscure. Of the series of 14 presented by Brean et al.,[4] seven patients suffered sudden death, three remained unreported and four are living. Brown and Evans[6] reported a feature complicating calcification in that their case had a spontaneous perforation through the center of the calcified infarct.

The susceptibility to sudden death of patients with massive myocardial calcifications should be interpreted with some caution. The fact that calcium was deposited in the scar proves that the infarct occurred in the distant past.

The case described below has certain interesting features. The primary myocardial insult occurred approximately 21 years previous to the finding of the calcification, and the electrocardiogram shows changes corresponding to the area of myocardial damage and calcification (figure 1). There is no evidence of myocardial failure, and the finding was incidental to a general medical study.

Case Report

The patient came into the author's office for a general medical study on March 10, 1953. The chief complaints were vague point pain over the precordium and in the region of the left lateral chest wall. This pain was unrelated to exertion. In 1932, approximately 21 years previously, the patient had been stricken by a heart attack. This was manifested by precordial pain, shock and loss of consciousness. He was hospitalized for six weeks. Except for the first few days, his recovery was

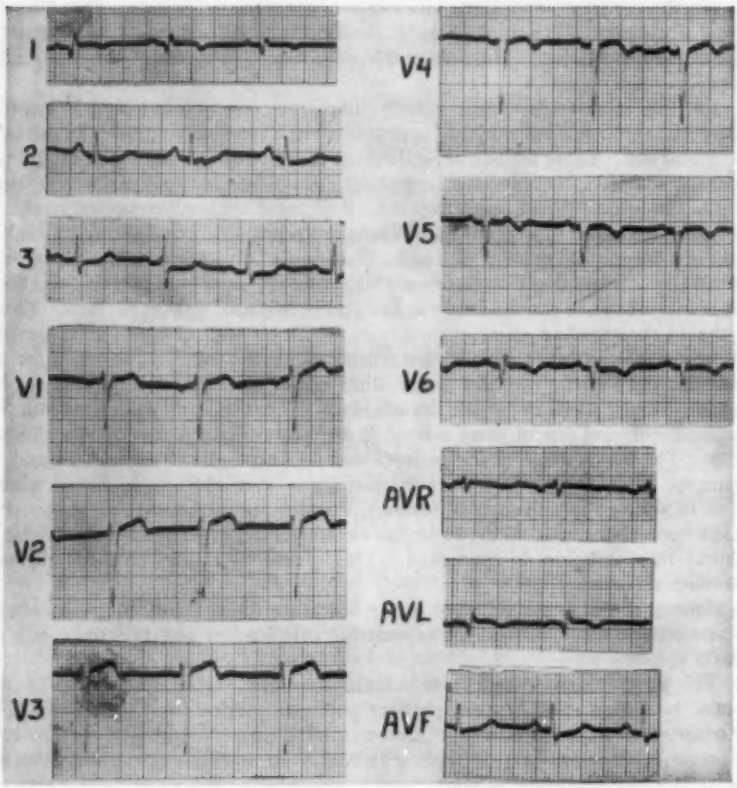

Fig. 1. Electrocardiogram taken March 10, 1953.

uneventful. Since the time of the original episode, the patient had lived an extremely virile life and had experienced good health. At the time of this writing he is approximately 52 years of age and carries on his duties as an executive with no evidence of physiologic impairment except for occasional brief episodes of vertigo which are spontaneous and unrelated to exertion. The inventory by systems is otherwise within the limits of normal. The patient is a heavy smoker and lives a very vigorous emotional and physical life.

Physical examination revealed the patient to be a well developed and well nourished Caucasian male of 158 pounds in weight and 68 inches in height. Temperature was 98.4° F.; pulse, 74 per minute; respirations, 20 per minute; blood pressure, right arm, 128/80 mm. of Hg; left arm, 130/80 mm. of Hg. The ocular fundi revealed a moderate grade one arteriosclerotic retinopathy. The skull, hair, face, ears, nose, mouth, neck, spine and thorax were within the limits of normal. Auscultation of the lungs presented sibilant rhonchi throughout the entire lung field which cleared

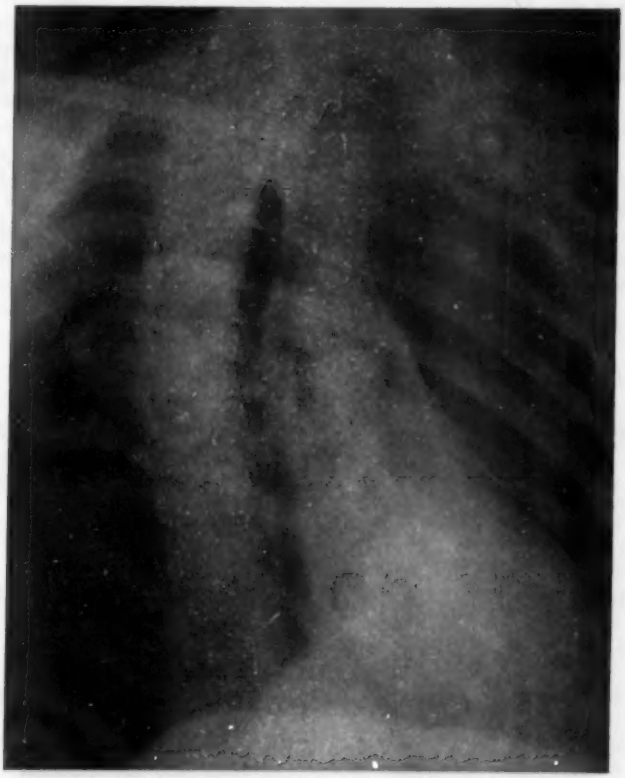

FIG. 2. Right anterior oblique view of the chest. This shows an oval calcification measuring 4.8 by 7.9 mm. located in the anterior portion of the left ventricle.

with cough. The heart presented the point of maximal impulse at the anterior axillary line at the fifth interspace. The heart tones at the apex were distant. A_2 was greater than P_2. No murmurs were audible. The abdomen was negative. There were no palpable cervical, axillary, inguinal or epitrochlear lymph nodes. The extremities were negative. Examination of the genitalia and proctoscopic examination to the six inch level were negative. Oscillometric studies of the calves revealed normal pressures. The dorsalis pedis and posterior tibial pulses were palpable.

An Exton-Rose blood glucose tolerance determination was normal. Urinalysis revealed normal findings. The hemogram was as follows: hemoglobin, 98.8 per cent or 14.7 gm.; erythrocytes, 5,000,000; mean corpuscular hemoglobin, 29.4; total leukocytes, 4,850; differential: neutrophils, 65 per cent (stabs, 2 per cent; segmented, 63 per cent); lymphocytes, 29 per cent; eosinophils, 1 per cent; and monocytes, 5 per cent. The sedimentation rate (Wintrobe) was 5 mm. per one hour. Urine calcium was 5 to 7.5 mg. per 100 c.c. Blood calcium determination was 10.0 mg. per cent. Alkaline phosphatase was 4.8 units (King-Armstrong). The blood Kline and Kolmer tests were negative.

FIG. 3. Tomograph made in the anterior-posterior projection at the 15 cm. level. The calcification involves more than half of the ventricular wall.

An electrocardiogram revealed the presence of a previous anterior and lateral myocardial infarction (figure 1).

Chest x-ray revealed an area of increased density in the apex of the heart. Fluoroscopy defined the presence of a large oval calcification measuring approximately 5 cm. by 7 cm. in the apex of the heart. Its anterior location placed it in the mid-portion between the right and left ventricles (figure 2). Laminagraphic studies of the heart defined the position of the calcification at the level of the left ventricle,

approximately midway between the anterior and posterior diameter of the mediastinum (figure 3).

An excretory urogram was normal.

Comment: Unfortunately, earlier x-ray studies are not available. However, the patient probably had a large anterior myocardial infarction in 1932 and this was followed by massive calcification. The unusual duration of physiologic normality following the original infarction and calcification is somewhat spectacular.

Whenever a history of myocardial infarction is obtained a roentgenographic study seems amply justified. The latter should also be performed in all cases of suspected heart disease, known heart disease and cardiac enlargement, and in all patients over 60 years of age.

Myocardial calcification as described above is only one of six types which may be classed as dystrophic and which involve the heart.[7] They are as follows: (1) Pericardial, which is usually the result of inflammation and occasionally tuberculous. (2) Valvular calcification. Mitral and aortic are most frequently calcified. It is rare to find the tricuspid similarly involved. (3) Calcification of the mitral annulus fibrosis. (4) Coronary artery calcification. (5) Myocardial calcification. This occurs most frequently near the apex. (6) Endocardial calcification.

Conclusions

1. A case of massive dystrophic myocardial calcification is presented.
2. The history is of approximately 21 years' duration, dating to the time of the possible original myocardial infarct, although there is no proof substantiating the exclusion of a silent infarct in the interval.
3. There is no evidence of physiologic impairment.

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SYSTEMIC SPREAD OF A CYSTIC DUCT CARCINOMA: A CASE REPORT *

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CARCINOMA of the cystic duct is a comparatively rare condition. Kirshbaum and Kozoll [3] found seven cases in 13,330 autopsies. Ferrar [2] reviewed the literature on this subject and claimed that up to 1951 only 31 cases had been reported and, according to Stewart, Lieber and Morgan (quoted by Ferrar), not all of them are fully acceptable. None of the 15 tumors of extrahepatic bile ducts reported by Willis [4] could be labeled as pure cystic duct carcinomas. Eleven involved the common duct only, three arose in the hepatic duct, and one involved the common duct as well as the hepatic and cystic ducts.

Ewing [1] found an early adenocarcinoma of the neck of the gall-bladder in the form of a pea-sized submucous nodule lying beneath practically unaltered mucosa, and suggesting an origin from aberrant gland tissue.

The purpose of this report is to present a case of cystic duct carcinoma widely metastasizing into the liver, lymph nodes, heart, spleen and bone marrow, and at the same time causing a difficult clinical diagnostic problem. This type of behavior of cystic duct carcinoma appears to be of rather uncommon occurrence, and no similar reference could be found in the recent literature.

The clinical course of the case to be presented lasted long enough to permit thorough medical and laboratory investigation, but in spite of it the exact nature of the disease remained obscure and the symptoms could not be explained until postmortem examination, after approximately five weeks of hospitalization.

CASE REPORT

A white man 73 years of age was admitted to the A. Barton Hepburn Hospital on August 16, 1952. His past history was irrelevant. More recently he had begun to seek medical advice. His doctor suspected heart or possibly gall-bladder disease. The patient had then been treated intermittently with digitalis, without, however, any beneficial subjective effect. During the last eight weeks he had lost 16 pounds. On admission he complained of a pain over the anterior part of his chest, radiating posteriorly and at times down both arms, aggravated by overexertion and only partially relieved by nitroglycerin. He also experienced intermittent attacks of dyspnea, gastric discomfort and flatulence after meals. He spoke of the insidious onset of the above symptoms, which began about one year prior to admission.

The physical examination revealed a well nourished, slightly obese man with distinct pallor of the skin. The examination of the heart and lungs was negative. On examination of the abdomen it was found that the lower margin of the liver extended about one and one-half fingerbreadths below the right costal margin. The spleen was just palpable. Rectal examination was negative. There were no neurologic signs.

The temperature was 100° F. on admission; it remained slightly elevated and

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remittent in type until August 24, after which it returned to normal. Blood pressure was 142/84 mm. of Hg; pulse, 118; respirations, 22 per minute.

Laboratory Findings:

Red blood corpuscles	2,670,000/cu.mm.
Hemoglobin	7.5 gm. (48%)
Color index	0.92
Leukocytes	7,500/cu.mm.
Differential leukocyte count (per cent)	
Polymorphonuclear neutrophils, total	64
Nonsegmented	17
Segmented	47
Lymphocytes	35
Eosinophils	1

The red blood corpuscles showed moderate anisocytosis and hypochromia.

Platelet count	59,400/cu.mm.
Sedimentation rate	61½ mm. in 1 hr. (uncorrected)
Corrected by hematocrit of 22%	13 mm. in 1 hr.

Blood Chemistry:

Glucose	285 mg. %
Nonprotein nitrogen	44 mg. %

Serum cephalin cholesterol flocculation test was negative.

Urinalysis: Showed 2 plus albumin and 2 plus glucose. Urine examination for Bence Jones protein was negative. Repeated stool examination revealed the presence of occult blood. The blood Wassermann reaction was negative.

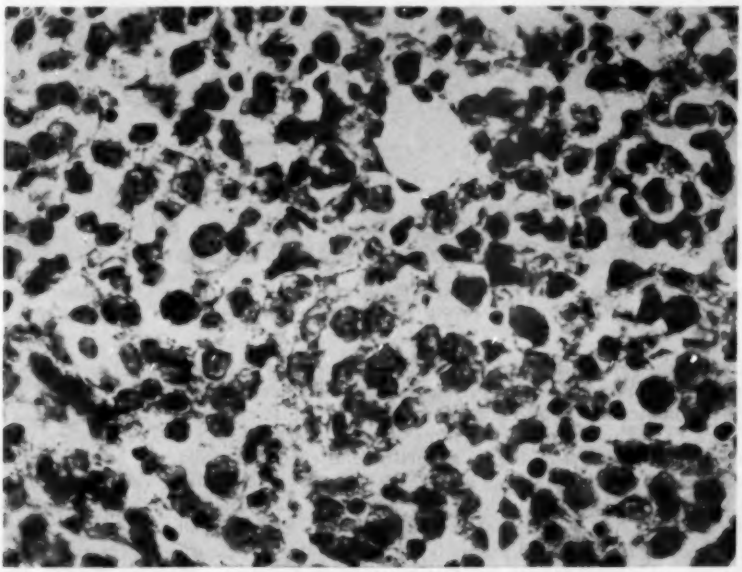

FIG. 1. Section represents the bone marrow biopsy, showing many large, atypical, undifferentiated cells of cancerous morphology; hematoxylin-eosin stain; × 525.

X-ray studies of the gastrointestinal tract revealed marked deformity of the duodenum, thought to be due to extrinsic pressure rather than to an intrinsic lesion. The gallbladder failed to concentrate the dye satisfactorily. Electrocardiogram showed evidence of left ventricular hypertrophy, sinus tachycardia and "digitalis effect" or early coronary artery disease.

The patient was placed on a diabetic diet and his blood sugar level was controlled by small doses of insulin. His chest discomfort was relieved to some extent by administration of nitroglycerin and opiates. Repeated blood transfusions, iron intake, vitamin B_{12} and dietary measures, however, did not effectively alter his anemic state. Because of the patient's undetermined and uncontrollable anemia a bone marrow biopsy was taken. Studies of the first pathologic slides revealed only patchy areas of

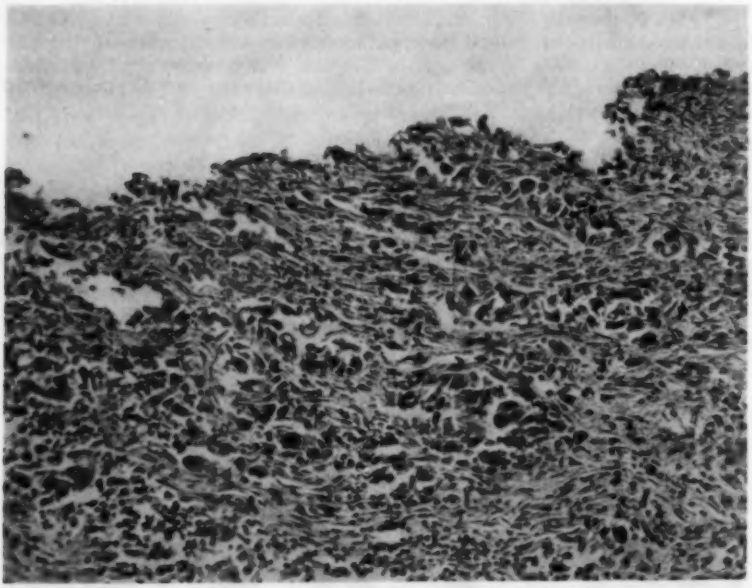

FIG. 2. Primary growth in cystic duct. The mucosa is absent. The wall is infiltrated with rather pleomorphic cancer cells; hematoxylin-eosin stain; × 145.

hyperplastic bone marrow. Later, serial sections were made and one or two foci were found where numerous large, hyperchromatic and undifferentiated cells were seen, densely infiltrating bone marrow spaces and replacing the normal marrow cells (figure 1). This picture was interpreted as a cancerous process, but in view of the fact that the cells were highly anaplastic the condition could not be satisfactorily classified. The possibility of aleukemic leukemia or metastatic cancerous deposits in bone marrow was considered. On September 12 a sudden elevation of patient's temperature (102° F.) was observed. His pulse was 122 and respirations were 34 per minute. He perspired profusely and complained of extensive anterior chest pain. The general clinical picture was that of coronary occlusion. He went steadily downward and died on September 19, 1952.

Autopsy (Abstract): Gross Examination: On external inspection many isolated petechiae scattered throughout the skin were observed. A small superficial hemorrhage was noted on the cornea of the left eye.

Internal Examination: The heart was enlarged and hypertrophied, weighing 520 gm.; the left ventricle particularly showed a conspicuous increase in size. On sectioned surface multiple areas of necrosis were evident scattered throughout the papillary muscles and myocardium of the left ventricle. These areas ranged from 0.3 cm. up to 0.7 cm. in diameter. They were irregular in shape, grayish pink in color, relatively soft in consistency, and often surrounded by a narrow rim of congestion. The main branches of the coronary arteries were opened and, apart from occasional flat atheromatous plaques, no other abnormalities were found.

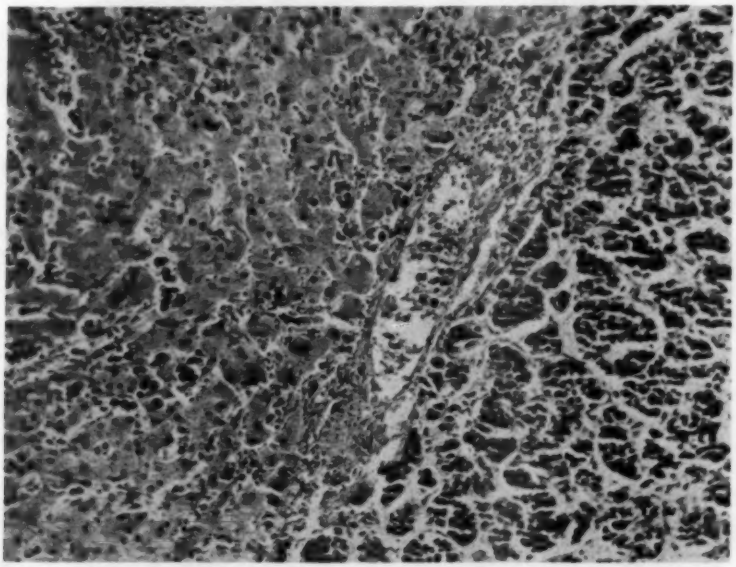

FIG. 3. Secondary deposit in the liver. The right side of the photomicrograph shows a solid mass of tumor cells arranged in groups and separated by thin bundles of connective tissue stroma. Some of the liver sinusoids contain cancer cells; hematoxylin-eosin stain; × 120.

The liver was enlarged, weighing 2,960 gm. It was softer than usual. Under the capsule as well as on the sectioned surface many small, well defined grayish nodules were found. They measured from a few millimeters up to 1 cm. in diameter.

The gall-bladder appeared collapsed. It contained a few cubic centimeters of inspissated bile and several small dark gall-stones. The gall-bladder was slightly edematous and its mucosa was flattened and smoothed out.

A small growth was found in the cystic duct, near the junction with the hepatic duct. It was situated under only moderately ulcerated mucosa but was causing sufficient pressure to result in an almost complete occlusion of the lumen. The neoplasm seemed to extend beyond the boundary of the cystic duct wall, and formed a collar-like thickening around the duct. On sectioned surface the growth was solid, rela-

tively soft in consistency and grayish pink in color. The lesion measured 1.2 cm. in longest diameter. Several enlarged and firm lymph nodes were found in the vicinity, as well as in the more distant locations, namely, around the pancreas and greater curvature of the stomach. This lymphadenopathy was more pronounced, however, in the nodes around the cystic duct. The remaining extrahepatic bile ducts were also examined but no abnormal changes were noted.

The spleen was found considerably enlarged, weighing 950 gm. Its capsule was tense and studded with numerous petechial hemorrhages. On sectioned surface the organ appeared soft in consistency and was a dark reddish gray.

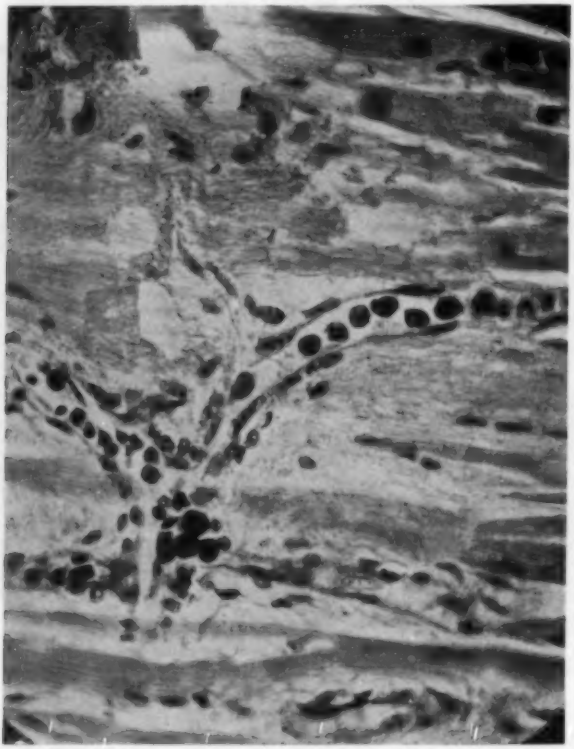

FIG. 4. Myocardium in the vicinity of a small infarct, showing minute arterioles packed with carcinoma cells; hematoxylin-eosin stain; × 375.

The bone marrow exposed in the middle shaft of the femur appeared dark red, with mottled areas of grayish yellow substance. In addition, a few grayish nodules were found embedded in the midst of the marrow pulp. These nodules were vaguely defined and soft in consistency, and measured up to 0.3 mm. in diameter.

The remaining organs and systems presented no gross abnormal findings.

Microscopic Examination: Cystic Duct: Sections taken from the lesion observed in the cystic duct revealed a necrotic or denuded mucosa and evidence of malignant

neoplastic condition invading the wall of the duct (figure 2). The new growth was composed of cylindrical, medium-sized cells with irregular large nuclei and prominent nucleoli. Some of the cells contained two nuclei. The mitotic figures were scanty. The more superficial areas were infiltrated with inflammatory cells. The tumor in some selected fields retained a pattern of moderately differentiated adenocarcinoma, particularly in areas more distant from the mucosal surface.

Liver: The secondary deposits in the liver were composed of closely packed and hyperchromatic groups of cells with only a vague alveolar arrangement, and were separated by a thin and delicate network of connective tissue. In addition, individual cancer cells were readily seen in sinusoids and between the liver cells (figure 3).

Heart: Figure 4 demonstrates an arteriole blocked by tumor cells. Many minute vessels similar to this one were seen in the midst of necrotic areas or in their vicinity.

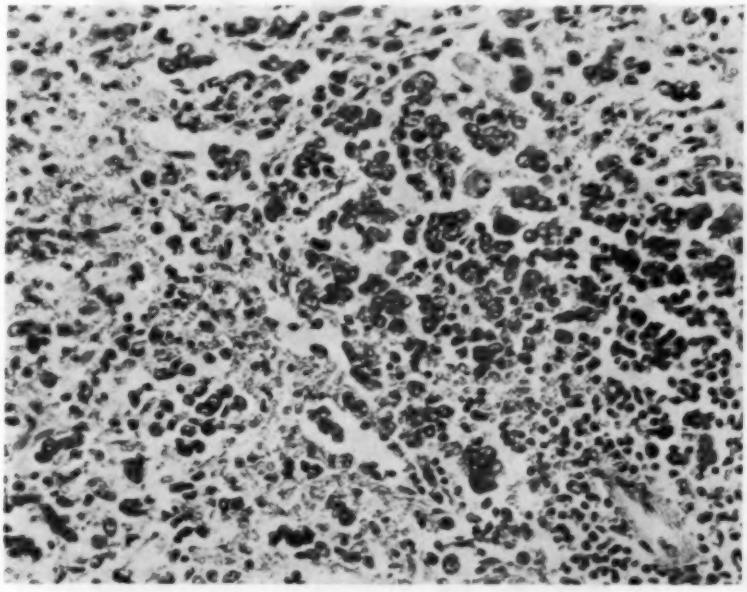

FIG. 5. Spleen. Groups of cancerous cells are seen scattered throughout the splenic parenchyma; hematoxylin-eosin stain; × 265.

It is evident that the tumor cells by blocking the lumina of precapillaries and arterioles were responsible for the occurrence of multiple myocardial infarctions.

Spleen and Lymph Nodes: The spleen, and the lymph nodes taken from the vicinity of the cystic duct, also presented a picture of invasion by neoplastic cells (figures 5 and 6). A photomicrograph of a lymph node is shown under higher magnification (× 605) for better demonstration of cancer cells intermingled with lymphoid cells (figure 6).

Bone Marrow: The material was taken from the middle shaft of the femur. It showed a great number of large hyperchromatic cancer cells, occasionally containing two large and well formed nuclei (figure 7). The picture was essentially similar to that observed in sections of bone marrow biopsy (figure 1), with the exception that

the staining qualities of neoplastic cells were more hyperchromatic than in marrow biopsy.

Comment

The clinical symptoms of the cystic duct carcinoma just described appeared to be similar to those generally observed in cancer of extrahepatic bile ducts. Kirshbaum and Kozoll,[3] in their clinicopathologic studies of 62 autopsied cases

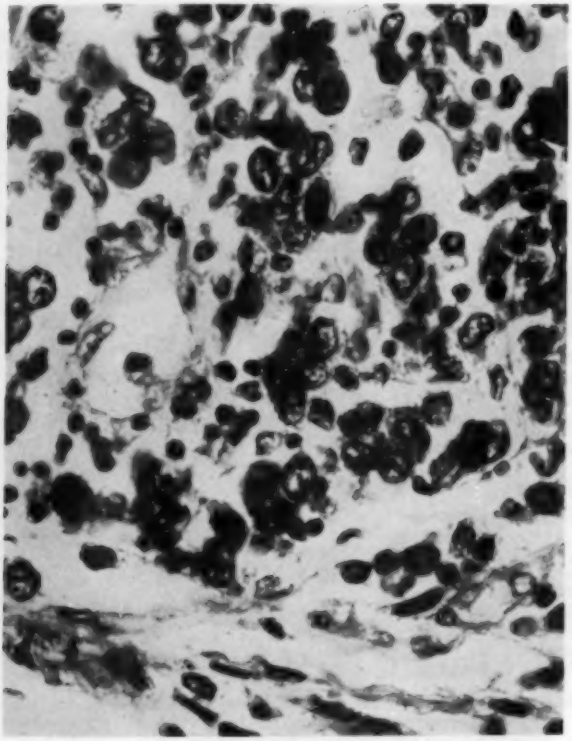

Fig. 6. Lymph node. Photomicrograph illustrates the cellular details of carcinoma cells. The nuclei are large, mostly oval; the chromatin is irregularly dispersed, chiefly at the periphery of the nuclei. The nucleoli are prominent; hematoxylin-eosin stain; × 605.

with carcinoma of the extrahepatic bile ducts, found that mild complaints referable to the gastrointestinal tract were surprisingly frequent. In 32 patients there were nausea, anorexia and vague dyspepsia. Constipation was more common than diarrhea. Severe secondary anemia was observed in 19 cases. Occult blood in stools was found in 55 per cent of these patients. The authors emphasized the diagnostic difficulty in primary carcinoma of the gall-bladder or extra-

hepatic bile ducts, particularly in so-called silent cases. Pathologically these neoplasms were classified as (1) infiltrative, (2) medullary, and (3) papillary. Willis [4] observed that most of his cases of extrahepatic biliary tract tumors represented "poorly differentiated adenocarcinomata." The sites of metastases varied from case to case. Willis [4] mentions seven cases out of 15 which spread into peritoneum, liver, lymph nodes and lungs.

In the cases of Kirshbaum and Kozoll,[5] secondary deposits were found on various occasions in the liver, lymph nodes, peritoneum, omentum, mesentery, extrahepatic bile ducts, gall-bladder, pancreas, duodenum, jejunum, pylorus, lungs, adrenal, kidney, pleura, rectum, spleen, diaphragm, seminal vesicle, skin of breast, pancreatic duct and ureter. None of the quoted authors observed

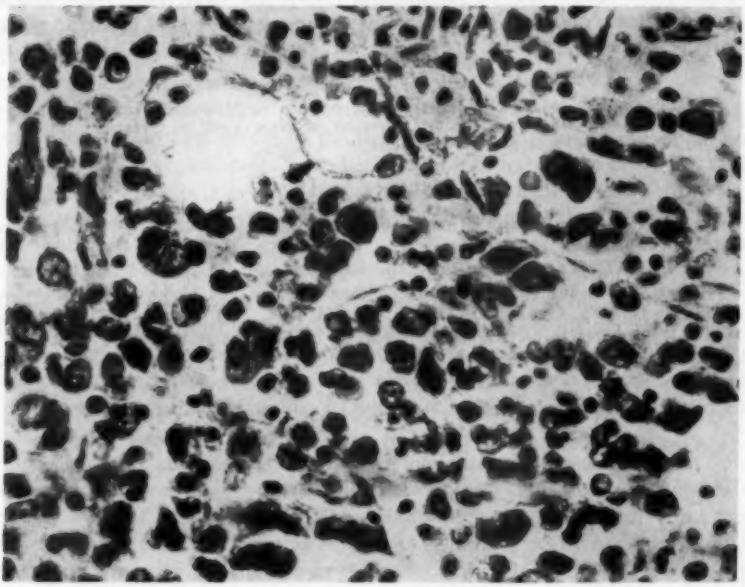

FIG. 7. Bone marrow (autopsy material from femur). The crowded carcinoma cells result in marked replacement of bone marrow tissue; hematoxylin-eosin stain; × 575.

metastases in the bone marrow and the heart. In fact, there was no reference as to whether, in any of these cases with severe anemia, the bone marrow was searched either by biopsy or during postmortem examination for possible evidence of suppression of hemopoietic system with cancerous deposits.

The presented case of primary cystic duct carcinoma seems to conform to the criteria proposed by Ferrar:[2] (1) The growth must be restricted to the cystic duct. (2) There must be no neoplastic process in the gall-bladder. (3) Histologic examination of the growth must confirm the presence of carcinoma cells.

Summary and Conclusions

A case is presented of primary cystic duct carcinoma with metastases into the liver, lymph nodes, heart, spleen and bone marrow. The clinical picture of this disease was manifested by progressive weakness, profound anemia, vague gastrointestinal disturbances, occult blood in stools and, terminally, by acute myocardial infarction. Bone marrow biopsy revealed a cancerous condition of unknown origin. The postmortem examination presented evidence that the main clinical symptoms and signs were a manifestation of the same process. The case was briefly commented upon in the light of some selected publications.

We believe that such a wide lymphatic and hematogenous spread of cystic duct carcinoma, which includes involvement of bone marrow and heart, and responsibility for severe anemia and multiple myocardial infarctions, represents an exceedingly rare condition, since no similar reference was found in the accessible recent literature.

Acknowledgment

The authors wish to acknowledge their appreciation to Miss Stella Zimmer, Head of the Department of Photography, State University of New York at Syracuse, College of Medicine, for preparation of photomicrographs.

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2. Ferrar, D. A. T.: Carcinoma of the cystic duct, Brit. J. Surg. **39**: 183–185, 1951.
3. Kirshbaum, J. D., and Kozoll, D. D.: Carcinoma of the gall bladder and extrahepatic bile ducts, Surg., Gynec. and Obst. **73**: 740–754, 1941.
4. Willis, R. A.: Some aspects of the pathology of carcinomata of the biliary tracts, M. J. Australia **2**: 340–344, 1942.

EDITORIAL

DIFFUSE INTERSTITIAL PULMONARY FIBROSIS

CHRONIC pulmonary disease as a cause of dyspnea and progressive disability presents many difficult clinical problems and has been less clearly delineated than the circulatory diseases which give rise to similar symptoms. Extensive fibrosis as a cause of pulmonary insufficiency appears in several different forms and may have many different causes. Recent studies have revived interest in one of the unusual types of fibrosis which was originally described in 1935 by Hamman and Rich,[1] who reported three cases [2] as fulminating diffuse interstitial fibrosis of the lungs. Although alerted to the existence of such cases, nine years elapsed before an additional case was recognized and the four cases more extensively described.[3]

Subsequent studies have confirmed the occasional but infrequent occurrence of cases corresponding to the description of Hamman and Rich, and in all at least 25 typical cases have been reported,[4] as well as about 10 to 20 others which are either incompletely described or which differ more or less significantly from the original description. In general the precision of the latter has been confirmed, with minor modifications and some amplification. In particular it has been shown that such cases often run a more protracted chronic course and that some of the clinically acute cases may really be long standing cases in a terminal stage of severe pulmonary insufficiency.

Although the clinical symptoms and roentgenologic features, at least in the more advanced stages, are fairly characteristic, they do not suffice to exclude other types of fibrosis. Diagnosis depends upon histologic examination (biopsy or autopsy).

Clinically the characteristic symptoms have been dyspnea, orthopnea and cyanosis, all increasing progressively in intensity until they become distressing even at rest. The patients finally die of suffocation, from respiratory insufficiency, unless this stage has been averted by prior fatal myocardial insufficiency. There may be thoracic pain, hemoptysis, and a paroxysmal cough which is usually nonproductive unless intercurrent infection occurs.

These severe symptoms may be preceded by a more or less protracted period of milder illness, vague ill health, fatigue, milder dyspnea on exertion, and a chronic, usually unproductive cough. Intercurrent respiratory infections presumably may accelerate the course of the disease, but a history

[1] Hamman, L., and Rich, A. R.: Fulminating acute interstitial fibrosis of the lungs, Tr. Am. Clin. and Climatol. A. **51**: 154–163, 1935.

[2] A fourth case was included in the original report but subsequently discarded as questionable.

[3] Hamman, L., and Rich, A. R.: Acute diffuse interstitial fibrosis of the lungs, Bull. Johns Hopkins Hosp. **44**: 177–212, 1944.

[4] Peabody, J. W., Jr., Buechner, H. A., and Anderson, A. E.: Hamman-Rich syndrome, A. M. A. Arch. Int. Med. **92**: 806–824, 1953.

of antecedent pneumonia or repeated respiratory infections is quite exceptional. Fever, leukocytosis or acceleration of the sedimentation rate occur as a rule only with intercurrent or terminal infections.

In the more advanced stages there is little or no respiratory reserve, and even a mild infection may precipitate a severe exacerbation of symptoms and a rapidly fatal outcome. The difficulty is not ventilatory but is due to interference with the exchange of gases resulting from disturbance of the pulmonary capillaries by the fibrous tissue in the alveolar walls. The oxygen saturation of the arterial blood falls, even at rest. In some of the more chronic cases secondary polycythemia has developed as well as clubbing of the digits.

The changes in the alveolar walls tend to obstruct the flow of blood through the pulmonary capillaries, in effect tend to narrow the capillary bed and raise the pulmonary arterial blood pressure. This leads to hypertrophy and dilatation of the right ventricle and in about half the cases to insufficiency of the right ventricle and the clinical manifestations of cor pulmonale.

Abnormal findings on physical examination are usually trivial and of little aid. The roentgenologic features are also not specific. An increase in density of the hilar and vascular markings is described, and eventually a bilateral diffuse reticular mottling with granular or nodular thickenings superimposed. If complicated by intercurrent infection or edema from right ventricular failure, the usual features of these conditions may be added.

The diagnosis has rarely been made ante mortem. Silverman et al.,[5] however, have reported one case diagnosed by biopsy of the lung. The diagnosis was suspected clinically because of the characteristic symptoms and radiologic signs, the normal ventilatory mechanism, the low arterial oxygen saturation, the high venous pressure, and the high pressure in the pulmonary artery and right ventricle (40 to 50 mm. Hg) on cardiac catheterization.

The course of the disease has varied greatly, the duration from onset of symptoms to death ranging from 31 days to three and a half years and even to nine years.[4] The acute cases with brief course probably represent merely the terminal stage of a much longer illness. In some instances the disease may apparently remain almost quiescent for a time, and activity may be reinstated by some intercurrent infection or other exciting cause. It is quite possible that clinical recovery or at least arrest may occur, but this has not been demonstrated. In most of the recognized cases the course has been relentlessly progressive, often rapidly so, and quite uninfluenced by any treatment thus far utilized.

Pathologically the lungs have been described in most cases as voluminous, heavy, firm, noncrepitant or subcrepitant, and sinking if placed in water. The pleural surfaces are usually uninvolved, but they may show fine ir-

[5] Silverman, J. J., and Talbot, T. J.: Diffuse interstitial pulmonary fibrosis camouflaged by hypermetabolism and cardiac failure: Antemortem diagnosis with biopsy and catheterization studies, Ann. Int. Med. **38**: 1326–1338, 1953.

regular depressed scars enclosing tiny emphysematous blebs. On gross section the lungs usually appeared dry, firm, granular, with fine fibrous strands forming a lacy network and giving the lungs a coarse texture. Some cases have shown varying degrees of edema and scattered areas of consolidation (terminal infection).

The most characteristic feature is detected only on microscopic examination and consists of a marked diffuse generalized thickening of the alveolar walls. In the early or acute stage, as described by Hamman and Rich, there is swelling, edema, and some deposition of fibrin in the alveolar walls, with often a moderate infiltration with mononuclear cells (lymphocytes and plasma cells) and varying numbers of eosinophiles. Neutrophilic leukocytes are sparse or absent, and no bacteria can be demonstrated by stain or culture in uncomplicated cases. Very quickly there occurs an active proliferation of young fibroblasts in the alveolar walls, with abundant deposition of fibrous tissue, which so markedly thickens the walls that they may encroach upon the alveolar spaces.

The epithelial cells lining the alveoli become enlarged, cuboidal, tend to desquamate and often undergo necrosis. Occasionally they may show so marked hyperplasia that they resemble pulmonary adenomatosis.[6] There is more or less outpouring of protein-containing fluid into the alveoli, and particularly if the cellular lining is desquamated and necrotic, it may form a hyaline membrane (fibrin) lining the walls. This feature was extraordinarily marked in the case of Callahan et al.[7] Hemorrhage into the alveoli may occur. There is, however, no appreciable inflammatory exudate in the alveoli in typical cases.

In more advanced stages the walls become further distended by fibrous tissue which is less cellular and "older" in appearance. Eventually both lungs become diffusely indurated by this fine meshwork of relatively acellular fibrous tissue. However, even in advanced stages areas can be found which show the exudative features of the early stage, indicating continued activity of the underlying disease. A striking feature is the absence (except in small foci) of organization of intra-alveolar exudate, in marked contrast to the usual types of organizing pneumonias.

This fibrosis disturbs the relation of the capillaries to the alveolar walls, it interferes with gaseous exchange, and in increasing degree it impedes the circulation in the pulmonary bed and raises pulmonary arterial pressure. Eventually there may be some degree of subintimal thickening of the arterioles, but this is secondary and not a feature of the syndrome. There may also be some fibrosis about the bronchioles and the larger vascular trunks, and this may result in tiny emphysematous blebs, but these are incidental and not characteristic of the disease.

[6] Rubin, E. H., Kahn, B. S., and Pecker, D.: Diffuse interstitial fibrosis of the lungs, Ann. Int. Med. **36**: 827–844, 1952.

[7] Callahan, W. P., et al.: Acute diffuse interstitial fibrosis of the lung, A. M. A. Arch. Int. Med. **90**: 468–482, 1952.

In previous reports hyperplasia of the capillaries has not been notable. Recently, however, Golden et al.[5] have reported that in three cases studied with a phase microscope and by special staining procedures, the thickening of the alveolar walls was due largely to hyperplasia of the capillaries. These are described as altered in arrangement and increased in size and number, in places forming from two to six layers. There was also a hyperplasia of the reticulin fibers which was usually marked, but fibroblasts were not notable and hyperplasia of collagenous fibrous tissue was inconstant and not an essential feature, although in one case it was marked. As these cases clinically and pathologically seem typical in other respects, the significance of this observation must await confirmation in additional patients.

The heart in the more chronic cases showed dilatation and hypertrophy of the right ventricle, which was sometimes very marked. Other pathologic lesions were variable and largely incidental.

The cause of the disease is not known. Ordinary bacterial infections of the lung can be excluded. Bacteria have not been demonstrated in the tissues, and nothing of significance has been obtained in cultures. The appearance of the tissues in the early stage suggests an inflammatory process, and it resembles to some extent that seen in some cases of influenzal pneumonia and primary atypical pneumonia. The most frequent suggestion has been that it may be due to a viral infection. There is no direct proof, and no inclusion bodies have been found. No relation can be shown to atmospheric irritants or to inhalation of foreign substances. Since the fibrosis somewhat resembles that seen in some cases of scleroderma and dermatomyositis, the possibility has been suggested that it is a localized form of a collagen disease. There is as yet no assurance that a single agent is responsible for all cases.

As might be anticipated, corticotropin and cortisone have been tried in a few cases, based partly on favorable results reported in some cases of sarcoid and berylliosis which showed a somewhat similar pulmonary fibrosis. No benefit has been reported except in one case in an early stage of the disease reported by Peabody et al.[4] This was a man of 31, with moderately severe symptoms of three months' duration, who was not helped by vigorous treatment with five antibiotics. Within a few days after corticotropin was started, there was substantial clinical improvement and a marked reduction in the density of the pulmonary shadows. A good remission was so maintained for over a month. A few days after gradual withdrawal of the hormones had been effected, however, a violent recurrence of symptoms occurred, films of the chest showed a return of the previous abnormal markings, and the patient died within 24 hours in spite of resumption of active treatment. Two other more advanced cases received similar treatment without appreciable improvement. When treatment was stopped or the dose notably reduced, there was a violent exacerbation of symptoms and

[5] Golden, A., and Bronk, T. T.: Diffuse interstitial fibrosis of the lungs, A. M. A. Arch. Int. Med. **92**: 606-614, 1953.

rapid progression to death within two weeks. In the few cases reported by others,[3, 4, 9] although treatment was not helpful, there appears to have been no special difficulty in terminating it.

As might be expected, these hormones seem ineffective after extensive fibrosis has occurred. They do not cause a removal of fibrous tissue after it has been formed. The initial benefit in the first case suggests that they may lessen the initial inflammatory reaction and prevent or delay fibrosis. However, the violent reactions occurring in these three cases on attempting to discontinue administration suggest that the dangers may outweigh any possible benefits. At least they necessitate extreme caution, administration should be restricted to early cases of marked severity unresponsive to other measures, and it should be started with the realization that hormones may have to be continued indefinitely. The problem of reaching an early diagnosis adds to these difficulties.

Diffuse interstitial fibrosis of the lungs—the "Hamman-Rich syndrome" [4]—is therefore an uncommon disease of unknown etiology, diagnosed with certainty only by histologic examination, which in its recognizable forms runs an unfavorable course uninfluenced by present methods of treatment. The problems are numerous, interesting and virtually untouched. It is obviously desirable that such cases be recognized in the early stages and that they be carefully studied and reported as opportunity offers. It is also evident that corticotropin and cortisone should not be used recklessly in patients with chronic pulmonary disease.

PAUL W. CLOUGH

[9] Cox, T. R., and Cole, J. M.: Diffuse fibrosing interstitial pneumonitis (interstitial fibrosis of the lungs), Am. J. Clin. Path. **22**: 770–776, 1952.

REVIEWS

The Diabetic Neuropathies. By Joseph I. Goodman, M.D., Siegfried Baumoel, M.D., Leonard Frankel, M.D., Louis J. Marcus, M.D., and Sigmund Wassermann, M.D. Edited by Willard O. Thompson, M.D., Clinical Professor of Medicine, University of Illinois College of Medicine, Chicago. Publication number 151, American Lecture Series, Monograph in Bannerstone Division of American Lectures in Endocrinology. 138 pages; 14.5 × 22 cm. Charles C Thomas, Springfield, Illinois. 1953. Price, $4.75.

This volume is noteworthy as the first American monograph, published as a bound volume, devoted to the problems of diabetic neuropathy. The authors compare the clinical findings in their subjects with the reports of others and point out that the incidence of this condition is determined by the diagnostic criteria employed for its detection. They have not attempted to apply qualitative or quantitative tests of vibratory perception in the study of their patient material, but they review much of the literature pertaining to its use.

Because the pathogenesis of diabetic neuropathy, its pathologic physiology, and the lesions associated with it are still poorly understood, the authors devote their major effort in this review to a thorough discussion of the subjective and objective manifestations of the disorder. These they group under sensory disturbances, motor weakness, absence of tendon reflexes, disturbances in autonomic function particularly genitourinary and gastrointestinal, neurogenic arthropathy, and cranial nerve lesions. Gastroenterologists, urologists, and orthopedic surgeons, as well as internists, will find this section informative.

The authors classify diabetic neuropathy into functional, organic, post-treatment, and neurovascular types. This division appears dependent on the circumstances under which the symptom of pain appears, whether in association with hyperglycemia or hypoglycemia, whether or not in association with clinically demonstrable arteriosclerosis, and whether or not in association with objective signs of neurologic deficit. They do not attempt to fit into this classification 39 (24 per cent) of their subjects who had absent ankle or knee jerks without symptoms. On reading material on pages 55, 105, and 111 this reviewer feels that they imply that although they consider loss of achilles tendon reflexes very reliable evidence of neuropathy in diabetic subjects, they deem the same loss not reliable evidence of sciatic or tibial nerve involvement.

Throughout the book the authors stress their disbelief in the arteriosclerotic theory of the genesis of the disorder primarily because they do not find a correlation between the incidence of clinically demonstrable arteriosclerosis in extremities involved by neuropathy; and because of the disappearance of pain following treatment and the return of muscle function in those few subjects in whom it has been impaired. Recent calorimetric and microplethysmographic technics have provided data interpreted as evidence for the existence of occlusive arterial disease in the extremities of younger diabetic subjects in whom the usual gross diagnostic tests fail to reveal circulatory impairment. It may be pertinent to apply such studies to the problem of diabetic neuropathy. The disappearance of pain may be part of the poorly understood natural history of the disorder rather than the result of treatment. Recovery of muscle function itself, when such loss occurs, may not be a result of treatment either. It is not too unusual to observe patients whose skeletal muscles have recovered much of their function following almost complete disability after a cerebral vascular accident.

The authors feel that neuropathy is "one complication of diabetes which can be prevented, or cured, provided it is treated sufficiently early," by control of the

diabetes. But later in their discussion they state that "in view of the lack of a yardstick to measure the results of therapy, the beneficial agent in the ultimate recovery from a condition as chronic as diabetic neuropathy is difficult to evaluate." Some of the apparent contradictions in this book doubtless may be attributed to the anxious hope that is apt to be engendered in those who are confronted with so distressing a condition as clinically severe diabetic neuropathy.

Even if these minor objections are sustained, this book is quite worth reading for the spotlight it casts on a little known, and heretofore less appreciated, but extremely widespread disorder.

P. F.

Diseases of the Endocrine Glands. By LOUIS J. SOFFER, M.D., F.A.C.P., Associate Attending Physician and Head of the Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital, New York City, etc.; with the assistance of J. LESTER GABRILOVE, M.D., Research Assistant, Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital; with the Section on Carbohydrate Metabolism, Hypoglycemia, and Diabetes Mellitus by HENRY DOLGER, M.D., Adjunct Physician for Metabolic Diseases; Physician in Charge of the Diabetic Clinic, The Mount Sinai Hospital; and the Section on the Gonads by ARTHUR R. SOHVAL, M.D., Adjunct Physician, and Member of the Endocrine Research Laboratory and Clinic, The Mount Sinai Hospital. 1142 pages; 24 × 15.5 cm. Lea & Febiger, Philadelphia. 1951. Price, $15.00.

Dr. Soffer and his collaborators have expanded his excellent monograph, *Diseases of the Adrenals,* into a textbook of endocrinology. In general, the result is a well documented volume, a sound and authentic compilation of the pertinent literature and of the authors' investigations. The discussions of the physiology of the endocrine glands, and of the pathogenesis of the various disease states resulting from their dysfunctions, are thorough and up-to-date. The clinical descriptions are good. On the whole, therapy is adequately covered. A chapter on laboratory tests of endocrine function is appended. Unfortunately, no introductory chapter of orientation in the broad field of endocrinology is included.

This volume, however, is not without faults. The use of the term "Simmonds' cachexia" as a synonym for panhypopituitarism seems ill advised, since it calls to mind the emaciated individual who more often than not turns out to have anorexia nervosa.

The section on the diseases of the parathyroids is sketchily treated. The advocacy of the use of parathyroid extract in the treatment of acute hypothyroidism is surprising and is not generally accepted.

The section on carbohydrate metabolism is well conceived and up-to-date. However, the frequent use of italics for emphasis is irritating and distracting. The treatment of diabetes mellitus leaves much to be desired. The whole subject of diabetic diets is poorly treated, and it is difficult to know what *is* recommended. Dietetic instructions and diet calculation and measurement are considered wasteful. It seems facetious to state that the diabetic diet is a normal diet except for the omission of sugar, pastry and soft drinks. On the other hand, a diet containing as little as 100 gm. of carbohydrate is advised in the initial stages of uncomplicated diabetes, presumably to avoid insulin. Fasting blood sugars of 200 mg. per cent, in the absence of gross glycosuria and with maintenance of adequate nutrition, are considered adequate control; this seems quite high. In the treatment of diabetic coma, the immediate use of glucose as advised here is a controversial point, while the restriction of gastric lavage to patients who are vomiting is open to serious question.

The text has not been well proof-read. The section on physiology of the adrenal medulla blends with that of the adrenal cortex without a major subheading. Several

pages on the relationship of the adrenal cortex to renal function are repeated virtually verbatim under the renal function in Addison's disease. The incidence of diabetes in inductees at Boston in the last World War is stated to be 4.6 per cent, instead of 0.46 per cent.

R. C.

Modern Trends in Gastroenterology. Edited by F. AVERY JONES, M.D., F.R.C.P. 831 pages; 17.5 × 25.5 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1952. Price, $20.00.

This is a British and Australian book, planned and edited by one of the outstanding and accomplished physicians of Great Britain. In it he has brought together recent work in the gastroenterological aspects of medicine and surgery. His contributors are British and Australian physicians, surgeons, and investigators who have presented admirably a great quantity of clinical material along with important original and fundamental material at the basic science level. Each of the authors has been pleasantly clear, concise, and complete.

The scope of this work is tremendous and this becomes even more remarkable when one considers the great detail with which each major subject has been handled. In many sections there are helpful practical guides and notes which reflect the authors' first-hand knowledge of their subjects.

Dr. Avery Jones has wisely included a separate chapter on functional or psychogenic disorders of the digestive system, in addition, of course, to the psychiatric considerations and remarks in other chapters concerned with specific disorders. Such an inclusion is of great value to the practitioner, for, as a rule, he sees a high proportion of patients with functional disorders of digestion. Despite this truth, many other textbooks have allocated only brief sections to these common functional ailments.

For these and many other reasons, this book deserves to become a favorite reference work. It is informative and stimulating.

W. C. E.

Spatial Vectorcardiography. By ARTHUR GRISHMAN, M.D., and LEONARD SCHERLIS, M.D., The Mount Sinai Hospital, New York. 217 pages; 20.5 × 28.5 cm. W. B. Saunders Co., Philadelphia. 1952. Price, $6.00.

A most important advance in the study of the electrical forces of the heart since the perfection of clinical electrocardiography is the development of spatial vectorcardiography. In conventional or scalar electrocardiography, each lead represents a projection of the electrical forces on a single axis, and a multiplicity of leads is used to obtain a detailed picture of the cardiac electrical forces. In spatial vectorcardiography, the electrical activity of the heart is represented as a single curve arrested in space; the electrocardiographic leads are considered as derivatives of this curve. Vectorcardiography, it is claimed, therefore offers a direct simple method of studying cardiac electrical forces in health and disease.

This monograph is designed to further the application of this new concept, and "to present those features of spatial vectorcardiography which make it a valuable adjuvant to clinical electrocardiography." The opening chapters deal with the basic theory of the genesis and spread of cardiac currents, and with the recording of these currents by conventional electrocardiographic and vectorcardiographic methods. The normal vectorcardiogram and its components are described. There are chapters devoted to left ventricular hypertrophy, left bundle branch block, right ventricular hypertrophy, right bundle branch block, and myocardial infarction. The authors have wisely attempted to give an over-all view of the field, rather than to present all the observations available or the numerous problems involved.

An unusual and valuable feature is the presentation of actual recorded vectorcardiograms and electrocardiograms as a basis for accomplishing its purposes, and it does so admirably. There is a transparent insert which may be placed over the vectorcardiograms to aid in visualizing the conventional scalar leads. This proves a useful device. The illustrations are well-reproduced. The text is clear, concise, and carefully organized.

This new book gives an unparalleled broad view of spatial vectorcardiography. It should be read with interest and profit by internists and cardiologists, and should serve to provide a new dynamic basis for the teaching and understanding of conventional electrocardiography as well.

S. S.

Antibiotics. 2nd Ed. By ROBERTSON PRATT, Ph.D., and JEAN DUFRENOY, D.Sci. (Paris). 398 pages; 16 × 24 cm. J. B. Lippincott Company, Philadelphia. 1953. Price, $7.50.

The appearance of the second edition of this book so early indicates its wide acceptance. This treatise on antibiotics is divided into four parts. Part I treats of the fundamental aspects of antibiosis, membrane diffusion, and the concept of threshold and optimal concentrations. In addition, it contains an interesting chapter on the requisites of an ideal antibiotic. Part II is concerned with the industrial aspects of the production of antibiotics—the methods of screening, manufacturing and assaying these products. Part III considers the individual antibiotics—penicillin, bacitracin, streptomycin, etc.—their antibiotic spectra, absorption, excretion, blood levels, and the phenomenon of acquired resistance on the part of bacteria. Part IV includes the modification of biologic and social systems. Here consideration is given to mutation, natural selection and adaptability. Also the mechanisms whereby the antibiotics kill susceptible organisms is discussed.

The most interesting aspect of the text is the chapter concerning social and economic aspects of the antibiotics. In this chapter the authors in a lucid style point out the impact that the discovery of these drugs may have on the composition of our ever-changing population. They point to the challenge for research in the degenerative diseases.

On the whole the book is a welcome addition to one's library in the field of antibiosis. It adequately covers the subject from various aspects, and is written with a felicity of diction that is engaging.

J. C. K., JR.

Introduction to the Interpretation of the Electrocardiogram. By LOUIS N. KATZ, M.D., RICHARD LANGENDORF, M.D., and ALFRED PICK, M.D., Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago. 78 pages; 19 × 23 cm. (paper-bound). The University of Chicago Press, Chicago. 1952. Price, $2.50.

This booklet is intended as a brief graphic outline of the more important electrocardiographic deviations from normal, and to introduce the student and practitioner to the subject of electrocardiography. The first seven pages are devoted to a good description of the genesis of the electrocardiogram, and the next three to a description of the principles and technic in obtaining an electrocardiogram. After this interesting but inadequate introduction to the subject, the reader is confronted with two and one-half pages on "procedure in reading an electrocardiogram," a two-page table of normal electrocardiographic characteristics, and 61 illustrations of electrocardiograms. This volume would not seem to serve any very useful purpose.

S. S.

Mother and Baby Care in Pictures. 4th Ed. By LOUISE ZABRISKIE, R.N., Director, Maternity Consultation Service, New York City. 244 pages; 15.5 × 23.5 cm. J. B. Lippincott Company, Philadelphia, Pa. 1953. Price, $3.00.

Advice to expectant mothers and guidance in child care are usually found in separate books. That the combination of these subjects in one book must be popular, is attested by the appearance of the fourth edition of this work. This unification is not without precedent when one remembers that single textbooks of yesteryear often embraced midwifery and the diseases of children.

Written for the laity by an eminently qualified author, emphasis throughout is placed upon the importance of nutrition to the mother and child in the prenatal and postnatal periods. New material in the present edition includes information on the following subjects: demand feeding, early ambulation, pregnancy tests, natural childbirth, the Rh factor, and rooming-in.

A number of new and excellent illustrations have been added. The type is clear and the text is in double column.

Placed in the hands of prospective parents, this book will serve as a most readable guide to prenatal care, labor and the puerperium, as well as a reference during the child's first year of life.

J. E. S.

BOOKS RECEIVED

Books received during January are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Acute Pulmonary Edema. Modern Medical Monographs 10. By MARK D. ALTSCHULE, M.D., Assistant Professor of Medicine, Harvard Medical School, etc. 68 pages; 22.5 × 14 cm. 1954. Grune & Stratton, New York. Price, $3.50.

Administrative Medicine: Transactions of the First Conference, March 9, 10 and 11, 1953, New York, N. Y. Edited by GEORGE S. STEVENSON, M.D., Medical Director, National Association for Mental Health, New York, N. Y. 176 pages; 23.5 × 15.5 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.00.

Das Analzäpfchen in der Geschichte der Therapie. By PROF. DR. P. DIEPGEN, Mainz. 43 pages; 23 × 15.5 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart; Agents for U.S.A.: Grune & Stratton, Inc., New York. Price, kart. DM 4.20.

The Chest: A Handbook of Roentgen Diagnosis. 2nd Ed. By LEO G. RIGLER, M.D., Professor and Chief, Department of Radiology, University of Minnesota. 380 pages; 21 × 14 cm. 1954. The Year Book Publishers, Inc., Chicago. Price, $8.00.

Connective Tissues: Transactions of the Fourth Conference, February 18, 19 and 20, 1953, Princeton, N. J. Edited by CHARLES RAGAN, M.D., Associate Professor of Medicine, Columbia University College of Physicians and Surgeons, New York, N. Y. 197 pages; 23.5 × 16 cm. 1953. Sponsored by the Josiah Macy, Jr. Foundation, New York, N. Y. Price, $3.75.

Dermatologic Medications. By MARGUERITE RUSH LERNER, M.D., Resident, Department of Dermatology; and AARON BUNSEN LERNER, M.D., Ph.D., Associate Professor of Dermatology, University of Oregon Medical School, Portland. 183

pages; 18 × 12 cm. (paper-bound). 1954. The Year Book Publishers, Inc., Chicago. Price, $3.50.

Disorders of the Blood: Diagnosis, Pathology, Treatment, Technique. 7th Ed. By SIR LIONEL E. H. WHITBY, C.V.O., M.C., M.A., M.D. (Cantab.), F.R.C.P. (Lond.), D.P.H., Regius Professor of Physic in the University of Cambridge, etc.; and C. H. C. BRITTON, M.D.(New Zealand), D.P.H., Physician and Haematologist to the Prince of Wales's Hospital, London, etc. 856 pages; 25 × 15.5 cm. 1953. Grune & Stratton, New York. Price, $9.50.

Eleven Blue Men and Other Narratives of Medical Detection. By BERTON ROUECHÉ. 215 pages; 21 × 14 cm. 1954. Little, Brown & Company, Boston. Price, $3.50.

An Introduction to Pathology and Bacteriology for Medical Students in the Tropics. 2nd Ed. By the late E. C. SMITH, B.A., M.D., D.P.H., Sc.D. Dubl., M.R.C.P. Lond., M.R.C.P.I., D.T.M. & H. Eng., Sometime Senior Pathologist, Medical Laboratory Service, Nigeria; revised by R. KIRK, O.B.E., B.Sc., M.D., D.P.H., F.R.F.P.S. Glas., M.R.C.P. Lond., F.R.S. Edin., Professor of Pathology in the Kitchener School of Medicine, University College of Khartoum. 390 pages; 25.5 × 16 cm. 1954. Staples Press, New York. Price, $9.00.

Joint FAO/WHO Expert Committee on Nutrition: Third Report. World Health Organization Technical Report Series No. 72. 30 pages; 24 × 16 cm. (paper-bound). 1953. Published jointly by FAO and WHO and issued also as "FAO Nutrition Meetings, Report No. 7." World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 20 cents.

Klinik der Nebenniereninsuffizienz und ihre Grundlagen. By PROF. DR. LUDWIG WEISSBECKER, with an introduction by PROF. DR. LUDWIG HEILMEYER. 251 pages; 24.5 × 16.5 cm. 1954. Ferdinand Enke Verlag, Stuttgart. Price, Geheftet DM 31.–; Ganzleinen DM 33.–

Klinische Zytologie: Grundriss der Allgemeinen Zytologie und der Zytodiagnostik. By H. J. STREICHER and ST. SANDKUHLER, with the assistance of OTTO A. ROTH and W. SCHWENKENBECHER. 195 pages; 24.5 × 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 49.80.

Le Leptospirosi. By PROF. DOTT. MARIO AUSTONI; preface by PROF. GINO PATRASSI. 715 pages; 24.5 × 17 cm. (paper-bound). 1953. Tipografia del Seminario, Padova. Price, 5000 Italian Liras ($8.00).

Maladies Médicamenteuses d'ordre Thérapeutique et Accidentel. By CLAUDE ALBAHARY; preface by A. TZANCK. 751 pages; 25 × 16.5 cm. 1953. Masson et Cie, Paris. Price, Broché 4.400 fr.; Cartonne toile 5.000 fr.

Medizin in Bewegung. By RICHARD SIEBECK. 493 pages; 25 × 18 cm. 1953. Georg Thieme Verlag, Stuttgart. Price, Ganzleinen DM 33.–

The Pathology of Trauma. 2nd Ed. By ALAN RICHARDS MORITZ, M.D., Professor of Pathology and Director of the Institute of Pathology of the School of Medicine of Western Reserve University, Cleveland, Ohio. 414 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $8.50.

Pharmacology and Therapeutics: A Textbook for Students and Practitioners of Medicine. 2nd Ed. By ARTHUR GROLLMAN, Ph.D., M.D., F.A.C.P., Lecturer in Pharmacology and Toxicology, The Medical Branch, and Professor and Chair-

man of the Department of Experimental Medicine, The Southwestern Medical School, The University of Texas, etc. 866 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $10.00.

Physiological Cardiology. Publication Number 184, American Lecture Series. By ARTHUR RUSKIN, M.D., F.A.C.P., Associate Professor of Internal Medicine, University of Texas—Medical Branch, Galveston, Texas; edited by ROBERT F. PITTS, M.D., Ph.D., Professor of Physiology and Biophysics, Cornell University Medical College, New York, New York. 370 pages; 22.5 × 14.5 cm. 1953. Charles C Thomas, Publisher, Springfield, Illinois. Price, $8.00.

Surgical Pathology. 2nd Ed. By PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College, etc. 893 pages; 24 × 15.5 cm. 1954. Lea & Febiger, Philadelphia. Price, $14.00.

Tercer Congreso Uruguayo de Cirugia, 1952, 1 al 7 de Diciembre. Sede: Hospital de Clinicas. 666 pages; 24.5 × 17 cm. (paper-bound). 1953. Secretaria General, Montevideo.

COLLEGE NEWS NOTES

New Life Members

The College is pleased to announce that the following Fellows have become Life Members since the publication of the last list in the January, 1954, issue of this journal:

Dr. Frank T. Moore, Akron, Ohio
Dr. Nathan Mitchell, Brooklyn, N. Y.
Dr. Maurice Nataro, Louisville, Ky.
Dr. Lawrence N. Irvin, Lima, Ohio
Dr. Grant O. Graves, Columbus, Ohio
Dr. Joseph F. Kuzma, Milwaukee, Wis.
Dr. Charles E. Gerson, Dayton, Ohio
Dr. William E. Molle, Los Angeles, Calif.
Dr. Alton F. Williams, Savannah, Ga.
Dr. Karl A. Menninger, Topeka, Kans.
Dr. Charles K. Donegan, St. Petersburg, Fla.
Dr. William G. Myers, Columbus, Ohio
Dr. Irving F. Burton, Detroit, Mich.
Dr. Wolcott B. Dunham, Memphis, Tenn.
Dr. David W. Scott, Jr., Fredericksburg, Va.
Dr. Elmer Russell Hayes, Dallas, Tex.
Dr. Elston L. Belknap, Milwaukee, Wis.
Dr. John L. Calene, Aberdeen, S. D.
Dr. James P. Croce, New York, N. Y.
Dr. Charles H. Kravitz, Philadelphia, Pa.
Dr. Benjamin E. Krentz, New York, N. Y.
Dr. Waldo B. Moyers, Mount Rainier, Md.
Dr. Harry E. Rollings, Savannah, Ga.
Dr. Chester M. Jones, Boston, Mass.
Dr. Bruce C. Lockwood, Detroit, Mich.
Dr. George Mason Parker, Peoria, Ill.
Dr. Henry B. Steinbach, Detroit, Mich.
Dr. Walter F. Donaldson, Bakerstown, Pa.
Dr. Lawrence F. Woolley, Atlanta, Ga.
Dr. Maxwell Berry, Atlanta, Ga.
Dr. Harold F. Brown, Buffalo, N. Y.
Dr. Marie L. Carns, Madison, Wis.
Dr. Frederick Hnat, Elizabeth, N. J.
Dr. Robert C. Kirk, Columbus, Ohio
Dr. Norval M. Marr, St. Petersburg, Fla.
Dr. Thomas M. McMillan, Philadelphia, Pa.
Dr. Ben N. Miller, Columbia, S. C.
Dr. George F. Strong, Vancouver, B. C., Canada
Dr. E. Richmond Ware, Los Angeles, Calif.

A.C.P. Regional Meetings

Eastern Pennsylvania Regional Meeting

The Eastern Pennsylvania Regional Meeting was held at Philadelphia, January 15, 1954, under the Governorship of Dr. Thomas M. McMillan, F.A.C.P. An even

300 doctors were in attendance, 269 from Pennsylvania, 15 from Delaware, 12 from New Jersey and one each from Florida, Louisiana, Utah and Mexico. Of the total attendance, 176 were members of the College. The Morning Session and luncheon were held at the College Headquarters, the Afternoon Session, Reception and Banquet were held at the Penn Sherwood Hotel. The Scientific Program was well received. The Banquet was addressed by Dr. Aims C. McGuinness, Dean of the University of Pennsylvania Graduate School of Medicine, on "The Responsibilities and Possibilities of Graduate Medical Education." Dr. George Morris Piersol, M.A.C.P., former President and former Secretary-General of the College, added a response, "Philosophy of the Educational Aims of The American College of Physicians."

Maryland-District of Columbia Regional Meeting

The Maryland-District of Columbia Regional Meeting was held at Baltimore, January 16, 1954, under the Chairmanship of Dr. R. Carmichael Tilghman, F.A.C.P., College Governor for Maryland, and with the coöperation of Dr. John Minor, F.A.C.P., College Governor for the District of Columbia. The meeting was conducted at Chemical Hall, University of Maryland. The Scientific Program was an especially fine one and was attended by a large proportion of the members in Maryland and the District of Columbia, with a gratifyingly large number of guests. A formal noonday luncheon was held at the Psychiatric Institute of the University of Maryland. Dr. Tilghman presided, Dr. Maurice C. Pincoffs, M.A.C.P., addressed the Meeting on "The Associate," Mr. E. R. Loveland, Executive Secretary, spoke on "The College: Its National and International Importance," and Dr. Jacob E. Finesinger, Professor of Psychiatry at the University of Maryland, spoke on "Educational Functions of the Psychiatric Institute." Unquestionably, this was the finest Regional Meeting of the College ever held in Maryland.

Colorado Regional Meeting

The Colorado Regional Meeting was held at the Broadmoor Hotel, Colorado Springs, January 22–23, 1954, in coöperation with the Colorado Society of Internal Medicine. Dr. C. F. Kemper, F.A.C.P., is the College Governor for Colorado. Dr. Dumont Clark, F.A.C.P., was Chairman of the Program Committee. There were approximately 175 members and visitors from Kansas, Nebraska, Wyoming, New Mexico and other nearby States. Dr. Philip S. Hench, F.A.C.P., Regent of the College, addressed the Banquet Meeting on "A Reminiscence of Certain Events Before, During and After the Discovery of Cortisone," and he also presented a paper on the regular scientific program. The Banquet was also addressed by Dr. Lawrence Holden, F.A.C.P., President of the Colorado Society of Internal Medicine. A part of the scientific program included a symposium on Immunologic Aspects of Hematology. Dr. William Creger of Stanford University, and Dr. Robert Evans of Seattle, were special guests on this portion of the program. This particular Regional Meeting appears to have been one of the most popular and worthwhile yet sponsored by our Colorado members, as evidenced by the fact that many have expressed the hope that a similar meeting be held in 1955.

Southern California Regional Meeting

A Regional Meeting surpassing all records for interest and quality of the scientific program of any past Southern California Regional Meeting, was held at Riverside, February 13–14, under the Governorship of Dr. Leland Hawkins, F.A.C.P., Los Angeles, and the Program Chairmanship of Dr. George C. Griffith of Pasadena. Dr. W. Philip Corr, F.A.C.P., of Riverside, was Chairman of Arrangements.

Among special guests who attended and who also spoke at the Banquet were Dr. Cyrus C. Sturgis, F.A.C.P., President-Elect of the College, Ann Arbor, Dr. George F. Strong, F.A.C.P., First Vice-President of the College, Vancouver, and Mr. E. R. Loveland, Executive Secretary, Philadelphia. The Meeting was held at the Mission Inn, and provided many entertainment features, both for the men and the ladies. A special feature of the Banquet was an address, "The Valley of Dry Bones," by Robert G. Cleland, Ph.D., LL.D., Litt.D., Professor of History; Director of the Study of Western American History at Huntington Library, San Marino, Calif. Probably no meeting in any region has done more to revitalize interest and activity in the College than did this one in Southern California.

Scheduled Regional Meetings

VIRGINIA at Richmond, February 25, Dr. Charles M. Caravati, F.A.C.P., Governor.
NEBRASKA at Lincoln, February 27, Dr. Joseph D. McCarthy, F.A.C.P., Governor.
KANSAS at Topeka, March 19, Dr. William C. Menninger, F.A.C.P., Governor.
SOUTHERN ILLINOIS at Peoria, March ?, Dr. Charles H. Drenckhahn, F.A.C.P., Governor.
NORTHERN CALIFORNIA and NEVADA at San Francisco, June 16, Dr. Stacy R. Mettier, F.A.C.P., Governor.
NORTH DAKOTA at Bismarck, September 11, Dr. Robert B. Radl, F.A.C.P., Governor.
NEW ENGLAND at Hartford, Conn., October 22, Dr. John C. Leonard, F.A.C.P., General Chairman and Governor.
WESTERN PENNSYLVANIA at Pittsburgh, October 27, Dr. C. Howard Marcy, F.A.C.P., Governor, and Dr. Roy R. Snowden, F.A.C.P., Chairman.
NEW JERSEY at Newark, November 3, Dr. Edward C. Klein, Jr., F.A.C.P., Governor.

A.C.P. Postgraduate Courses

In the advertising section of this issue is a full schedule of Postgraduate Courses for the Spring of 1954. The detailed Postgraduate Bulletin was sent on February 1 to all members of the College and to non-members on the mailing list. Copies are available to others on request.

Autumn, 1954, Tentative Schedule

INTERNAL MEDICINE: Medical College of Virginia, Richmond; Dr. Charles M. Caravati, F.A.C.P., Director; October 4–8.
INTERNAL MEDICINE: University of Oklahoma School of Medicine, Oklahoma City; Dr. Wann Langston, F.A.C.P., Director; October 4–8 (dates subject to change).
RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE: Mount Sinai Hospital, New York; Dr. Arthur M. Master, F.A.C.P., Director; October 11–15.
SELECTED SUBJECTS IN INTERNAL MEDICINE: University of Pittsburgh School of Medicine, Pittsburgh; Dr. Roy R. Snowden, F.A.C.P., Director, and Dr. Frank Gregg, F.A.C.P., Co-director; October 25–30.
GASTRO-ENTEROLOGY: University of Pennsylvania Graduate School of Medicine, Philadelphia; Dr. Henry L. Bockus, F.A.C.P., Director; November 15–19.
CARDIOLOGY: Michael Reese Hospital, Chicago; Louis N. Katz, F.A.C.P., Director (date to be announced).

INTERNAL MEDICINE: Beth Israel Hospital, Boston; Dr. Herrman L. Blumgart, F.A.C.P., Director (date to be announced).

MEDICAL ASPECTS OF NEOPLASTIC DISEASES: Memorial Center for Cancer, New York; Dr. Cornelius P. Rhoads, F.A.C.P., and Dr. Rulon Rawson, F.A.C.P., Co-directors (date to be announced).

PHYSIOLOGICAL BASIS OF INTERNAL MEDICINE: University of Pennsylvania Graduate School of Medicine, Philadelphia; Dr. Julius H. Comroe, Jr., F.A.C.P., Director (date to be announced).

A.C.P. Course in Ballistocardiography

The first course in Ballistocardiography, sponsored by the College, was given on January 11 to 13, 1954, at The Johns Hopkins Hospital under the direction of Dr. Benjamin M. Baker, Jr., F.A.C.P. Fifty-one physicians attended the course and they were enthusiastic in expressing their approval of the excellence of the material presented. The instructing group gave a very conservative evaluation of the subject and counseled a word of caution in regard to the clinical interpretation and application of ballistocardiographic records. The course included a background of the development of ballistocardiography and the technical aspects of current methods. The basic physical principles involved were carefully considered. The errors and pitfalls in the interpretation of the records and the projected possibilities for the future development of newer methods were discussed.

A.C.P. Offers Postgraduate Scholarships to Residents

Through a grant from Mead Johnson and Company, accepted by the Board of Regents of the College on November 14, 1953, the American College of Physicians will administer a limited number of postgraduate scholarships to internes or residents (preferably the latter) in Internal Medicine. The established fund provides an amount of $1,000.00 for the period of one year to needy residents in Internal Medicine. Nominations to the College must be made by the College Governors for the several states or territories. The list of College Governors appears elsewhere in this issue.

A.C.P. Group Health and Accident Insurance Plan

The first anniversary of the American College of Physicians Group Health and Accident Insurance Plan is almost here. April 15, 1954, will mark the date when the number of members participating in the Plan made it possible to announce that the Master Policy was in force.

Since then the number of certificate holders has grown until at this writing more than 3,200 members of the College have submitted applications, a very gratifying response to the program that was merely the germ of an idea in the spring of 1952.

Many hours of intensive study by the Insurance Committee of the Board of Regents and the Executive Secretary of the College of the accident and health Plans of similar organizations and the proposals of insurance companies resulted in the selection by the Board of Regents of Educators Mutual Insurance Company, Lancaster, Pa., as the insurance carrier and the Agency of Ralph O. Claypoole, Sr., and F. Wells McCormack, Philadelphia, to represent the insurance company.

Almost as soon as the first certificates of insurance were received by participating members of the College, requests for claim forms and notifications of illnesses and accidents began to arrive at the Association Service Office, Philadelphia, which was selected to administer the details of the A.C.P. Plan. Actually the first claim was received 6 hours after the announcement of the Plan at the 1953 Atlantic City Con-

vention from one of our members in attendance at the Meeting. To date 250 of the certificate holders have made claims for benefits.

During the Annual Meeting of the Board of Regents in November, 1953, the Insurance Committee and the Executive Secretary of the College met with Messrs. Claypoole and McCormack and made a comprehensive review of the handling of the College Group Health and Accident Insurance Program. All phases of the claims, applications and insurance company relationships were examined and found to be satisfactory. It was gratifying to the Insurance Committee that our members carefully and conscientiously completed their applications for insurance and claims, which resulted in a minimum of delay in issuing certificates and in the payment of claims.

New members of the College elected since April, 1953, have all been sent detailed information about the Plan and many have enrolled. Many members have requested an opportunity to enroll since July 11, 1953, the date when the Initial Installation Period ended. The College and Messrs. Claypoole and McCormack have opened negotiations with the insurance company to "re-open" the Plan. This will enable members who have not previously submitted applications to secure this protection on the same basis as during the Initial Installation Period. More about this will be provided next month. Meanwhile if there are any questions that any member desires answered about the Health and Accident Plan, the Association Service Office, 1500 Walnut St., Philadelphia 2, Pa., will give members prompt service.

Three postgraduate courses in pediatric cardiology are to be offered twice during 1954 by the Cook County Graduate School of Medicine, presented by Benjamin M. Gasul, M.D., Attending Pediatrician and Director of the Cardiac Division of the Cook County Children's Hospital, Egbert H. Fell, M.D., Attending Surgeon, Cook County Hospital, and associates. The courses will be intensive and practical, and are designed for the pediatrician, internist, general practitioner and roentgenologist. Examination of patients and the detailed study of case histories will utilize the wealth of clinical material available.

Course I—The Diagnosis and Treatment of Congenital and Rheumatic Heart Disease in Infants and Children, one week starting April 19 and October 18, 1954.

Course II—Roentgenology and Electrocardiography in Heart Disease in Infants and Children, three days starting April 26 and October 11, 1954.

Course III—Angiocardiography and Catheterization of the Heart and Great Vessels in the Diagnosis of Congenital and Acquired Malformations in the Hearts of Infants and Children, three days starting April 29 and October 14, 1954.

For information, address: Registrar, 707 South Wood Street, Chicago 12, Illinois.

Chest Disease Symposium for General Practitioners at Saranac Lake This Summer

The Third Annual Symposium on Tuberculosis and Other Chronic Pulmonary Diseases for General Practitioners, sponsored by the American Trudeau Society, the Saranac Lake Medical Society and the Adirondack Counties Chapter of the New York State Academy of General Practice, will be held at Saranac Lake, New York, from July 12 through 16, 1954. It is approved by the American Academy of General Practice for 26 hours of formal credit for its members.

Included in the course will be discussions of the diagnosis and treatment of nontuberculous pneumonias, pulmonary cancer, lung abscess, fungus diseases, bronchiectasis, sarcoid, cystic disease, emphysema, and the pneumoconioses. Many of the sessions will be informal panel discussions with ample opportunities for questions from the audience.

The speakers and panel members at the Symposium will include 34 physicians, surgeons, and scientists from Saranac Lake and surrounding areas. Guest lecturers include Dr. D. Ewan Cameron, Professor of Psychiatry, McGill University, Montreal, and Dr. Donald Miller, Assistant Professor of Thoracic Surgery, University of Vermont College of Medicine, Burlington.

The Symposium will be held in various sanatoria and laboratories in the Saranac Lake area. Morning sessions will be from 8:30–12:30 and afternoon sessions from 2:00–4:00 (Monday, Wednesday, and Thursday). There will be elective sessions on Tuesday and Friday afternoons. Physicians desiring to make patient rounds will have that opportunity each afternoon at 4:00.

Complete information concerning this program can be obtained by writing to Richard P. Bellaire, M.D., Chest Disease Symposium, P. O. Box 2, Saranac Lake, N. Y.

1954 Meeting, American Goiter Association

The 1954 meeting of the American Goiter Association will be held at the Somerset Hotel, Boston, Mass., April 29, 30 and May 1, 1954. The program for the three-day meeting will consist of papers and discussions dealing with the physiology and diseases of the thyroid gland.

The Second Congress of the Sociedad de Medicos Internos, Residentes y Becarios of the National Institute of Cardiology of Mexico will be held at Acapulco, Mexico, April 21–24, 1954, as a climax to the celebration of the Tenth Anniversary of the Foundation of the International Institute of Cardiology. Information and programs may be obtained from Dr. Jorge Soberón Acevedo, Secretary General of the Sociedad, Avenida Cuauhtemoc No. 300, Mexico, D. F.

National Foundation for Infantile Paralysis Announces Fellowships

The National Foundation for Infantile Paralysis announces the availability of a limited number of postdoctoral fellowships in the field of public health and preventive medicine. The purpose of these National Foundation fellowships is to prepare physicians to fill the many vacancies existing in public health and preventive medicine, with priority to those who are interested in entering the teaching field.

The fellowships are for one or more years at an approved school of public health, with a period of field experience when arranged by the school. Stipends to Fellows are based on the individual need of each applicant. Fellowships may cover tuition, maintenance and an allowance for books, if required. Appropriations of $320,600 in March of Dimes funds have been made to cover the cost of the program.

Eligibility requirements include United States citizenship, sound health, graduation from an approved school of medicine and completion of at least a one-year internship in an approved hospital. Selection of candidates will be made on a competitive basis by a Clinical Fellowship Committee composed of leaders in the fields of medicine and professional education.

In addition there are also available a limited number of postdoctoral clinical fellowships in physical medicine and rehabilitation to candidates who wish to become eligible for certification in that field.

Fellowships in this field will cover a period of one to three years at training centers which have been approved for residencies in physical medicine and rehabilitation. Stipends to Fellows are based on the individual need of each appli-

cant. Appropriations of $475,000 in March of Dimes funds have been made to cover the cost of the program.

Eligibility requirements include United States citizenship, graduation from an approved school of medicine, completion of at least a one-year internship in an approved hospital, and a license to practice medicine in at least one state. The age limit is 40. Selection of candidates will be made on a competitive basis by a Clinical Fellowship Committee composed of leaders in the fields of medicine and professional education.

In addition to these full-term fellowships, the National Foundation is making available a limited number of short-term fellowships to physicians who wish to become better acquainted with physical medicine and rehabilitation as it relates to their particular specialties. Such training is being offered to physicians who, in addition to meeting the other requirements, have completed a minimum of one-year residency in orthopedics, pediatrics, neurology or internal medicine. For these fellowships, which will cover a period of training of three months to one year at centers which place special emphasis on physical medicine in relation to the applicant's specialty, the National Foundation has provided a special appropriation of $51,050.

Complete information concerning qualifications and applications for these fellowships may be obtained from the Division of Professional Education, National Foundation for Infantile Paralysis, 120 Broadway, New York 5, N. Y.

Joint Commission on Accreditation of Hospitals

The Annual Meeting of the Commission was held on Dec. 5, 1953. The report of the activities of the field representatives, since Jan. 1, 1953, was discussed and approved. Assurance was received from the Canadian Medical Association that it is ready to employ a physician to be added to the list of those already carrying on the surveys of hospitals. With this addition the representation of all the organizations participating in the Commission will be complete, as the College already has taken steps to furnish the services of a physician for this work.

Certain changes in the Standards of Hospital Accreditation were discussed, and a committee was appointed to study the approach and procedure to be used in altering the Standards. Various changes in the wording of certain of the Standards were taken up, and a minor change suggested by the Committee on Consultations was adopted. A careful interpretation of the Standard dealing with the Dental Staff was reported by the appropriate committee headed by Dr. Middleton, and this report was adopted. The details of these actions have been published by the Director, Dr. Edwin L. Crosby, in the December issue of the Bulletin of the Commission.

In the election of officers for 1954, Dr. Newell W. Philpott was elected Chairman, Dr. LeRoy H. Sloan, F.A.C.P., Vice Chairman, and Mr. Stuart K. Hummell, Treasurer.

Since the Annual Meeting, the final figures covering the field work of the representatives of the Commission for the year 1953 have become available. There were 1,247 hospitals surveyed, of which 948 were recommended for Full Accreditation, 190 for Provisional Accreditation, 108 for No Accreditation, and action on one was deferred.

Army's Modified Affiliation Plan for Hospitals

More than fifty medical colleges and large civilian hospitals throughout the United States have entered into an informal agreement with Maj. Gen. George E. Armstrong, F.A.C.P., Army Surgeon General, whereby each will furnish a limited number of highly qualified doctors and dentists for key specialist assignments in a

1,000-bed general hospital for employment only in time of a major national emergency, the Department of the Army has recently announced.

This agreement is a modification of the reserve hospital plan used in World Wars I and II, under which a formally organized group was required to conduct military training, and secure a full complement of commissioned officers. The modified arrangement permits the hospital or medical school to retain these key professional staff members, selected for the unit for several months following the initial impact of the emergency. These personnel would not be required until after the reserve hospital units had been called to active duty and the administrative and housekeeping personnel organized and trained.

The colleges or hospitals in this "gentlemen's agreement" will not be required to provide a formal organization, appoint officers or agree to conduct training programs in order to be accepted in the plan. The modified affiliation plan, however, does not permit an officer to use it as a basis for military deferment if he should be called separately for active duty prior to the activation of the sponsored unit.

Many members of the College contributed to the success of the Fiftieth Annual Congress on Medical Education and Licensure, held in Chicago, Feb. 7–9. Drs. John C. Leonard, F.A.C.P., Hartford, Conn., and Ford K. Hick, F.A.C.P., Chicago, discussed "A Sound Program for Graduate Training in Non-University Hospitals" from the hospital and educational viewpoints, respectively. Dr. Walter L. Bierring, F.A.C.P., Des Moines, Iowa, delivered the "Report of the Secretary-Treasurer and Editor of the Federation Bulletin." Dr. Willard C. Rappleye, F.A.C.P., New York City, spoke on "The Educational Component of Medical Licensure," and Dr. S. Howard Armstrong, Jr., F.A.C.P., Chicago, discussed "The Relation of the Hospital Internship to Licensure." Dr. Louis H. Bauer, F.A.C.P., New York City, spoke of the activities of the American Medical Education Foundation, of which he is President. Dr. Roscoe L. Pullen, F.A.C.P., Columbia, Mo., participated in a panel discussion on "The Objectives of Postgraduate Medical Education," and Dr. Mahlon Delp, F.A.C.P., Kansas City, Kans., was among those who discussed "How to Achieve These Objectives." Dr. Franklin D. Murphy, F.A.C.P., Kansas City, Kans., summarized the discussion of the panel on "The Three 'F's': Facilities, Faculty, and Finance; The Requirements of Postgraduate Programs," of which Dr. Frode Jensen, F.A.C.P., New York City, was a member. Dr. Edward L. Turner, F.A.C.P., Chicago, was the speaker on Feb. 8 at the banquet of the Federation of State Medical Boards of the United States. Dr. George W. Covey, F.A.C.P., Lincoln, Nebr., read a paper on "Is Osteopathy a Cult?" Dr. Walter L. Bierring, F.A.C.P., and Dr. J. J. Moore, F.A.C.P., Chicago, were among those who delivered the "Report of First World Conference on Medical Education." Dr. Charles A. Doan, F.A.C.P., Columbus, Ohio, was one of those who gave the "Report of Committee on Licensure Problems."

Dr. Irving S. Wright, F.A.C.P., New York City, College Governor for Eastern New York and past President of the American Heart Association, was the principal speaker at the official opening of the Heart Exhibit at the Franklin Institute, Philadelphia, Jan. 29. Dr. Charles L. Brown, F.A.C.P., Dean of Hahnemann Medical College and Hospital of Philadelphia, presided. The Exhibit is a joint project of the Heart Association of Southeastern Pennsylvania, the Division of Adult Cardiovascular Diseases of the Commonwealth of Pennsylvania, and the Franklin Institute. It is 17½ feet high and 28 feet long, including the lungs. Once in it, an individual traverses the path of a corpuscle.

The Fourteenth Annual Congress on Industrial Health, sponsored by the Council on Industrial Health of the American Medical Association, was held in Louisville,

Ky., Feb. 24–25. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, College Regent, participated in a panel discussion, "Stress and Success—A Medico-Social Problem of Modern American Life." Dr. Lemuel C. McGee, F.A.C.P., Wilmington, College Governor for Delaware, presided at Section I on Wednesday afternoon. Dr. Oscar A. Sander, F.A.C.P., Milwaukee, presided at Section II, "Emphysema—Occupational Aspects of a Common Clinical Finding." In this section Dr. Frank Princi, F.A.C.P., Cincinnati, discussed "Therapy." At the annual dinner held that evening, Dr. J. Murray Kinsman, F.A.C.P., Louisville, College Governor for Kentucky, discussed "Rehabilitation in Louisville." At the concluding session on Thursday, which was held jointly with the Council on National Emergency Medical Service, Dr. John J. Phair, F.A.C.P., Cincinnati, talked on "Bacterial Warfare."

Dr. Frederick A. Johansen, F.A.C.P., Long Beach, Miss., was presented with a distinguished service plaque by the American Legion Auxiliary at the recent national convention in St. Louis. The citation read: "Dr. Frederick A. Johansen—in Appreciation of his Devoted Service to the Sick and Unfortunate and his Furtherance of a Better Understanding of Hansen's disease and its Treatment. Presented at the 1953 National Convention, St. Louis, Mo., American Legion Auxiliary." Dr. Johansen was for many years Medical Officer in Charge of the U. S. Public Health Service Hospital (National Leprosarium) at Carville, La.

Major Gen. Harry G. Armstrong, F.A.C.P., the Surgeon General, U.S.A.F., was recently awarded the Military Medal of Chile in recognition of his "valuable services to the Chilean Air Force and to all humanity" and for his assistance in giving Chilean students an opportunity to train at the U.S.A.F. School of Aviation Medicine.

The Philadelphia Metabolic Association recently presented its First Annual J. Howard Reber Memorial Medal to Dr. Randall G. Sprague, F.A.C.P., Rochester, Minn., for his contributions to the work in the field of diabetes.

Meeting in Baltimore, Md., Nov. 9, 1953, the National State and Territorial Health Officers Association honored Dr. Robert H. Riley, F.A.C.P., Baltimore. The Arthur T. McCormack Award which was given him emphasized that his contributions "have been a guide for health officers throughout the country in planning the organization and administration of medical services which have strengthened the total program of public health." Maryland Director of Public Health for the last 25 years, Dr. Riley joined the State Health Department in 1914, and from 1920–25 he served as Director of the Bureau of Communicable Diseases. He was named State Director in 1928, and in 1939 the Maryland Legislature appointed him to a life term in this office.

Dr. O. H. Perry Pepper, M.A.C.P., Philadelphia, was honored in the November, 1953, issue of the *Medical Clinics of North America*, the Philadelphia Number. The dedicatory foreword stated in part: "The contributions contained in this volume represent the admiration, respect and affection in which you are held by those whom you have influenced during the 45 years of your professional life. Their name is legion." A former Regent of the College, Dr. Pepper served as President during 1939–40, and is a member of the Editorial Board of the *Annals of Internal Medicine*.

Dr. Charles Pokorny (Associate), Halstead, was named President-Elect of the Kansas Trudeau Society at a recent meeting in Kansas City.

Dr. Edward S. Ray, F.A.C.P., Richmond, was elected President of the Virginia Trudeau Society at the organizational meeting in Richmond on Dec. 12, 1953.

Dr. Frank P. Pignataro, F.A.C.P., Red Bank, has recently been elected President of the New Jersey Neuropsychiatric Association.

At the recent meeting of the Georgia Heart Association, Dr. Joseph C. Massee, F.A.C.P., Atlanta, was elected President, and Dr. Ellison R. Cook, III (Associate), Savannah, was chosen President-Elect. Dr. J. Lamont Henry, F.A.C.P., Atlanta, is Secretary of the Association.

After serving 4 years as a member of the Council, Dr. George F. Evans, F.A.C.P., Clarksburg, took office on Jan. 1 as First Vice President of the West Virginia State Medical Association.

Dr. Sydney Jacobs, F.A.C.P., New Orleans, has recently been named Vice President of the Southern Trudeau Society.

At the annual meeting of the Kentucky State Medical Association, Dr. Woodford B. Troutman, F.A.C.P., Louisville, was reëlected to a 5-year term as Treasurer.

The Michigan Allergy Society recently elected Dr. Donald S. Smith, F.A.C.P., Pontiac, and Dr. Joseph H. Shaffer, F.A.C.P., Detroit, President and Vice President, respectively.

Dr. Walter Beckh, F.A.C.P., San Francisco, was elected President of the California Society of Internal Medicine at its recent annual meeting in Yosemite National Park. Dr. Paul I. Hoagland, Jr. (Associate), Pasadena, was chosen Vice President, and Dr. James H. Thompson, F.A.C.P., San Francisco, was made Secretary-Treasurer.

Dr. Martin S. Buehler, F.A.C.P., Dallas, has recently been elected President of the Texas Academy of Internal Medicine, and Dr. Samuel A. Shelburne, Sr., F.A.C.P., Dallas, was made a member of the Board of Governors.

Dr. George H. Coleman, F.A.C.P., was recently elected Secretary of the Institute of Medicine of Chicago. Dr. Henry T. Ricketts, F.A.C.P., is Chairman of the Board of Governors.

At its annual meeting in November, 1953, the New York Allergy Society chose Dr. William B. Sherman, F.A.C.P., New York City, as President-Elect, and Dr. Samuel J. Prigal, F.A.C.P., New York City, as Treasurer.

Dr. G. Harvey Agnew, F.A.C.P., Toronto, was elected President of the American Association of Hospital Consultants when it met in Bethesda, Md., in December. Dr. Jack Masur (Associate), Washington, D. C., was chosen Vice President.

Dr. Edward Kupka, F.A.C.P., Chief of the Bureau of Tuberculosis Control, California State Department of Public Health, has been granted a 10-year leave of absence in order to work with the Foreign Aid Program. During 1954 to 1955, he will be the Public Health Advisor to the Vietnam Government and will be headquartered at Havre.

Dr. Dickinson W. Richards, Jr., F.A.C.P., New York City, presented the 68th Mary Scott Newbold Lecture before the College of Physicians of Philadelphia on Jan. 6. His title was "Physiologic Behavior and Therapeutic Use of Plasma Volume Expanders."

Dr. G. Harvey Agnew, F.A.C.P., Toronto, discussed "Developments in Physical and Chemical Research (Including Atomic Research) Which Have a Relationship to Hospital Laboratories" at a joint meeting of the American Association of Hospital Consultants and the American Association for the Advancement of Science, which met in Boston on Dec. 30, 1953. At the same meeting, Dr. Jack Masur (Associate), Washington, D. C., spoke on "Varieties of Laboratory Service in Hospitals." In conjunction with the meeting of the American Association for the Advancement of Science, Alpha Epsilon Delta sponsored a luncheon Dec. 29, 1953, at which Dr. James M. Faulkner, F.A.C.P., Dean, Boston University School of Medicine, spoke of "The Need for More Well Qualified Applicants for the Medical Schools."

Dr. Samuel M. Feinberg, F.A.C.P., Chicago, discussed "Allergy to Chemotherapy" in a Symposium on Acute Infectious Diseases, sponsored by the California Academy of General Practice and Lederle Laboratories and held at Coronado, Calif., Dec. 9, 1953.

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., President-Elect of the College, delivered the E. Stanley Emery Memorial Lecture at the Peter Bent Brigham Hospital, Boston, on Jan. 13. His subject was "The Nature and Treatment of Leukemia and Allied Disorders."

Dr. Eugene A. Stead, Jr., F.A.C.P., Durham, N. C., presented the annual Henry J. Sewall Lecture at the University of Colorado School of Medicine, Denver, on Jan. 28. In addition, Dr. Stead conducted a series of conferences and laboratory discussions at the School of Medicine during the week of Jan. 25.

Dr. Joseph F. Hughes, F.A.C.P., Philadelphia, Pa., delivered the first in a series of lectures sponsored by the Hartford (Conn.) Medical Society. His topic on Jan. 18 was "The Practical Approach to Treatment of Anxiety." On March 1, Dr. Theodore E. Woodward, F.A.C.P., Baltimore, talked on "The Diagnosis and Management of Diseases of the Aseptic Meningitis Type," and on March 15, Dr. Edward H. Rynearson, F.A.C.P., Rochester, Minn., discussed "Clinical Disturbances Produced by the Over-function and Under-function of the Pituitary Gland." Lecturers still to be heard include Dr. Israel Steinberg, F.A.C.P., New York City, who will talk about "Angiography" on April 5, and Dr. Edward F. Bland, F.A.C.P., Boston, who will speak on "Indications for Surgery in Valvular Heart Disease: With Specific Reference to Mitral Stenosis" on April 19.

Dr. Louis N. Katz, F.A.C.P., Chicago, Director of the Cardiovascular Department of Michael Reese Hospital, discussed "The Implication of Recent Studies in Atherosclerosis" at a joint meeting of the Academy of Medicine of Cincinnati and the Heart Council on Jan. 19.

At the Seminars in Hematology sponsored by the Mount Sinai Hospital, New York City, Dr. Maurice B. Strauss, F.A.C.P., Boston, discussed the "Clinical Aspects of Vitamin B_{12}, Folic Acid, and Citrovorum Factor," Feb. 17. Dr. Leandro M. Tocantins, F.A.C.P., Philadelphia, participated in a panel discussion on "Hemophilia"

on March 17, and Dr. Lawrence E. Young, F.A.C.P., Rochester, N. Y., will discuss "Advances in Knowledge of Hemolytic Anemia" on April 21.

Dr. James W. Haviland, F.A.C.P., Seattle, Wash., has recently been appointed Acting Dean of the University of Washington Medical Department until a successor is appointed for Dr. Edward L. Turner, F.A.C.P., who resigned to become Secretary of the A.M.A. Council on Medical Education and Hospitals. Dr. Haviland has formerly been Assistant Dean.

Dr. Alan Lieberman, F.A.C.P., Elgin, Ill., retired Nov. 30, 1953, as Clinical Director of Elgin State Hospital to enter private practice. A state welfare employee for 15 years, Dr. Lieberman will remain on the staff as Consultant in Psychiatry.

Dr. John Severy Hibben, F.A.C.P., Pasadena, Calif., has announced his retirement from active practice after 36 years of continuous practice in Internal Medicine. He was formerly the City Health Officer, through the influenza epidemic in 1918, and more recently, Chairman of the Committee on Physical Medicine and member of the Senior Staff, Collis P. and Howard Huntington Memorial Hospital, a member of the Senior Staff of St. Luke Hospital and physician to the Medical Department of the Atchison, Topeka and Sante Fe and Union Pacific Railroads. He is a Diplomate of the American Board of Internal Medicine and has been a Fellow of the American College of Physicians for several years. A group of friends recently presented him with a testimonial, citing his achievements as a public official and as a private physician and useful citizen.

The Northern California Society of Allergy elected the following officers for the year 1954: Lazarre John Courtright, M.D., F.A.C.P., President; Edward Matzger, M.D., F.A.C.P., Secretary-Treasurer.

OBITUARIES

DR. DONALD T. CHAMBERLIN

Dr. Donald Tillinghast Chamberlin, F.A.C.P., who was born Feb. 21, 1905, in St. Louis, Mo., died Oct. 1, 1953, at his home in Knoxville, Tenn.

The fact that he was a wonderful student of medicine is shown by the many years of training he had had. After receiving an A.B. from Washington University, he entered the Medical School in the same University, graduating with an M.D. in 1930. A summary of his postgraduate work and private practice is as follows:

Intern, Massachusetts General Hospital (Boston) and University of Chicago Clinics, 1930–32; additional postgraduate training at Public Health Institute of Chicago (syphilis), 1933–34, Johns Hopkins Hospital (internal medicine), 1935–36, and Lahey Clinic (gastroenterology), 1936–37; Assistant Physician, New England Baptist and Deaconess Hospitals (Boston), 1937–41. Served from June, 1941–August, 1943, as Major (MC) AUS, and was Chief, Gastro-intestinal Section, Lawson General Hospital, Atlanta, Ga., and as Lieutenant Colonel, Chief of Medical Service of 750-bed hospital overseas. Following World War II was Assistant in Medicine, Harvard Medical School; Associate Physician-in-Chief and Consultant in Gastro-enterology, Malden (Mass.) Hospital; Gastro-enterologist, Newton-Wellesley, Cambridge City, and St. Elizabeth's (Boston) Hospitals; Consultant in Gastro-enterology, Addison-Gilbert (Gloucester) Hospital; Physician, Outpatient Department, Boston City Hospital; Member of courtesy staff, Framingham Union and Massachusetts Women's (Boston) Hospitals; Attending Physician, Cushing Veterans Administration Hospital (Framingham); Consultant in Gastro-enterology, U. S. Public Health Service. Since 1951, Attending Physician, Knoxville General, St. Mary's Memorial, Fort Sanders, and East Tennessee Baptist Hospitals; Member of Staff, Acuff Clinic; Consultant to the Surgeon General, U. S. Army and Consultant in Medicine, U. S. Veterans Administration.

He became a Diplomate of the American Board of Internal Medicine, member of the American Gastro-Enterological Society, American Medical Association, New England Medical Association, Southern Medical Association, and Knoxville Academy of Medicine; he was a Fellow of the Royal Society of Medicine (England) and of the American College of Physicians since 1945.

In the death of Dr. Chamberlin, the physicians of Tennessee feel that they have lost an outstanding man in internal medicine and an authority in gastro-enterology. During the three years he was in Tennessee, he made many friends. He was a fine person to know and a man greatly respected for his ability.

W. C. CHANEY, M.D., F.A.C.P.,
3rd Vice President, A.C.P.

DR. HARRY T. FOLEY

Dr. Harry Thomas Foley, II, F.A.C.P., died in Pittsburgh, Sept. 20, 1953, of coronary occlusion. Dr. Foley was born in Philadelphia, May 23, 1905.

He attended the University of Pittsburgh, receiving the degree of B.S. in 1926 and that of M.D. in 1929. Following an internship in the Medical Center Hospital, he was made Associate in Medicine; and in 1939 he became an Instructor in Medicine in the School of Medicine of the University.

Dr. Foley was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Cardiology and the American Geriatrics Society; he became a Fellow of the American College of Physicians in 1949. He was a member of the Aero Medical Society, the American Diabetic Society and the American Heart Association. After serving as a Captain (MC), AUS, in World War II, he

was appointed Special Civil Service Examiner and Civil Aeronautics Examiner for the Department of Commerce.

It is with real regret that the passing of Dr. Foley is herewith recorded.

C. Howard Marcy, M.D. F.A.C.P.,
Governor for Western Pennsylvania

DR. MARVIN LEE GRAVES

Dr. Marvin Lee Graves, a Fellow of the American College of Physicians, died at the Methodist Hospital, Houston, Tex., on Nov. 19, 1953.

Dr. Graves was born in Bosqueville, Tex., March 26, 1867. In 1885 he was granted the A.B. degree and in 1886 the M.A. degree, both from Southwestern University, Georgetown, Tex. The following two years were spent as a teacher in and principal of the public schools in Belton, Tex. He then began the study of medicine and received his M.D. from Bellevue Hospital Medical College, New York, in 1891. Following graduation he entered the practice of medicine at Waco, Tex., where he remained until 1898 when he moved to San Antonio to become Superintendent of the then Southwestern Insane Asylum. During the seven years he was connected with that institution, he became intensely interested in the problems of mental health. Not only did he acquire a complete familiarity with the major psychoses, but he was among the earliest to develop a correct appreciation of the clinical aspects of psychosomatic disorders.

In 1905 Dr. Graves was named Professor of Medicine and Lecturer on Mental and Nervous Diseases at the University of Texas, Medical Branch, in Galveston. He served in that capacity for twenty years, resigning his professorship in 1925 when he moved to Houston, where he entered the practice of Internal Medicine. During the years he was with the Medical School in Galveston, he was one of the most generally loved teachers in the institution by both faculty and students alike. At the beginning of his tenure, clinical teaching was done largely by didactic methods, and as a lecturer, Dr. Graves was outstanding. However, he soon became dissatisfied with the antiquated educational techniques employed, and under his aegis the clinical clerkship, modeled on the system of the German universities, was introduced. He was a tireless searcher for the newer concepts in medicine in general and in medical education in particular. Most of his summers were spent in postgraduate study in the great medical centers, including one in the University of Berlin. From all of these contacts he derived inspiration which he passed on to those around him. He was especially adept at assigning a responsibility to a younger associate, helping him in every way possible—but never driving him—and giving all the credit of accomplishment to the younger man. Through those with whom his professorship brought him into close touch, he exerted a profound influence on the medical thinking of his time in his area. Dr. Graves resigned as a Professor of Medicine at the peak of his career, so fearful was he of the dangers of remaining too long.

In Houston Dr. Graves, because of his many professional friends, did a large consultation practice in Internal Medicine. Yet he found time and had the energy and enthusiasm to be of assistance in many civic projects, in church work, and as a counsellor in numerous activities, both lay and medical. In later years his major interest developed in the field of the medical aspects of life insurance. He became Director and later Chairman of the Board of the American General Life Insurance Company.

Membership in medical societies included his county society, the Texas Medical Association, Southern Medical Association, Association of American Physicians, American Society of Tropical Medicine, and American Genetic Association. He was a member of the Phi Chi medical fraternity and of Alpha Omega Alpha. He was admitted to Fellowship in the American College of Physicians in 1926.

In the passing of Dr. Graves, Texas has lost one of her most distinguished citizens and Texas Medicine, its great philosopher, scholarly physician and, as he is affectionately remembered by many, "The Dean of Internal Medicine in Texas."

CHARLES T. STONE, M.D., F.A.C.P.

DR. CHARLES H. LUTTERLOH

Charles Hartzell Lutterloh, M.D., F.A.C.P., of Hot Springs, Ark., was born in Jonesboro, Ark., Oct. 13, 1897, and died of coronary thrombosis Oct. 30, 1953, at the age of 56.

Dr. Lutterloh was a graduate of St. Charles Military Academy, St. Charles, Mo.; he received his B.S. degree from the University of Arkansas and graduated from Tulane University of Louisiana School of Medicine in 1921. He interned at Touro Infirmary, New Orleans, and Memphis General Hospital, Memphis, Tenn. He practiced at Jonesboro from 1923 to 1931, and at Hot Springs from 1931 until shortly before his death.

He became a Fellow of the American College of Physicians April 4, 1932, and a Diplomate of the American Board of Internal Medicine July 1, 1937. Dr. Lutterloh was Clinical Professor of Medicine, University of Arkansas School of Medicine; Consultant in Medicine, Army and Navy General Hospital, Hot Springs, and the Veterans Administration Hospital, Little Rock; he was also a member of the staff of the St. Joseph's Hospital and the Leo N. Levi Memorial Hospital, Hot Springs.

He was past President of the Hot Springs-Garland County Medical Society, Arkansas State Board of Medical Examiners, and Mid-South Post Graduate Assembly.

He was a member of the American Medical Association, Southern Medical Association, American Society for Clinical Investigation, New York Academy of Sciences, American Society for the Study of Arteriosclerosis, American Diabetic Association, American Heart Association, American Geriatrics Association, American Rheumatism Association, and American Association for the Advancement of Science. He was a member of Lodge No. 129, F. & A. M., Royal Arch Mason, Knight Templar, Shriner, and Scottish Rite, and had served on the Board of Stewards of the First Methodist Church of Hot Springs for six years.

Dr. Lutterloh served in World War I as a private in the Student Army Training Corps, University of Arkansas, being discharged on Nov. 26, 1918. He became Assistant Surgeon in the Naval Reserve on July 14, 1932, with the rank of Lieutenant, j.g. After being honorably discharged he served as Examining Physician for the Garland County Selective Service System from Aug. 2, 1941. He entered the United States Air Force Sept. 15, 1942, with a commission of Major. After transferring to the Army of the United States, he was promoted to Lieutenant Colonel March 18, 1944, and was discharged Jan. 3, 1946.

Dr. Lutterloh contributed a number of scientific papers to medical literature and was very active in the civic life of his community and state, having served as State Chairman of the Easter Seal Campaign for the Arkansas Association for the Crippled in 1948. His family, colleagues, patients and friends will mourn the passing of Dr. Lutterloh, and he will be remembered as a good friend, good companion and a good man.

A. A. BLAIR, M.D., F.A.C.P.,
Governor for Arkansas

DR. CARL MULKY

Dr. Carl Mulky, F.A.C.P., died Jan. 14, 1954, of rheumatic heart disease. Dr. Mulky was born in Knoxville, Iowa, July 27, 1877. He received his pre-medical education at Iowa State University, and the degree of M.D. from Chicago Homeopathic Medical College, 1900, and Rush Medical College, 1901.

Dr. Mulky was an outstanding phthisiologist of the Southwest and practiced his specialty in Albuquerque for 33 years. He was kind, sympathetic and understanding to all his patients. The State of New Mexico has lost a fine citizen who devoted a great deal of his time and energy without reimbursement to organize a successful fight against tuberculosis.

Dr. Mulky served as a Captain in the United States Medical Corps in World War I. He was a Past President of the Bernalillo County Medical Society, the New Mexico Medical Society, and the New Mexico Tuberculosis Association. He was a Fellow of the American Medical Association and of the American College of Chest Physicians. He had been a Fellow of the American College of Physicians since 1931. He served as Chief Consultant to the State Tuberculosis Sanatorium at Socorro and the Veterans Administration Hospital in Albuquerque. He was a member of the active staff of the Southwestern Presbyterian Sanatorium and was on the associate staff of St. Joseph Sanatorium and Hospital.

Dr. Mulky was a member of the Masonic Lodge and its affiliated bodies. He was especially interested in the Shrine work, being a Past Potentate of the Ballut Abyad Temple. It is with sincere sorrow and regret that Dr. Mulky's colleagues and many friends record his passing.

WALTER I. WERNER, M.D., F.A.C.P.,
Governor for New Mexico

CAPTAIN CLARENCE W. ROSS

Captain Clarence Wesley Ross, (MC), USN, retired inactive, F.A.C.P., died Oct. 2, 1953, at the Naval Hospital, San Diego, Calif. His age was 67.

A great-grandson of John Ross, a Major in George Washington's Continental Army, Captain Ross was born at Lebanon, Ore., Jan. 14, 1886. He attended the University of Oregon, receiving his Bachelor of Arts degree in 1907 and his Doctor of Medicine degree in 1912. After two years in the practice of medicine in the State of Oregon, he accepted an appointment as an Assistant Surgeon, Medical Reserve Corps, USN, July 17, 1914. He transferred to the regular component of the Navy Medical Corps in 1915. He was promoted to Captain, (MC), USN, on July 1, 1939.

Prior to World War I, Captain Ross served at the Navy Yard, Mare Island, Calif.; at the Naval Medical School, Washington, D. C.; and aboard the *USS St. Louis* and *USS Maryland*. During the Mexican Campaign, he served on the *USS Yorktown*, performing gunboat patrol duty in Mexican and Central American waters. During World War II, Captain Ross served as Commanding Officer of the Naval Hospitals, Balboa, C. Z.; New Orleans, La.; and Mare Island, Calif.; and as District Medical Officer, Fourth Naval District, Philadelphia, Pa.

During his more than 35 years of Naval service, he also served on the United States Ships *Brooklyn*, *Charleston*, *Curlew*, *Savannah*, and *Arctic;* as Senior Medical Officer on the hospital ship, *USS Relief;* and ashore at the Naval Hospitals, Great Lakes, Ill.; San Diego, Calif.; and Pearl Harbor, T. H.

Captain Ross was a Diplomate of the American Board of Internal Medicine, a Fellow of the American College of Physicians since 1936, and a member of the American Medical Association. He was placed on the Retired List of Officers of the Navy on Feb. 1, 1948, but was immediately recalled to active duty. He was released to inactive duty on March 31, 1950.

Interment was in Fort Rosecrans National Cemetery, San Diego, Calif.

Technical Information Center,
Bureau of Medicine and Surgery,
Navy Department.

Fig. 1 "Roentgen examination . . . revealed the ulcer to be very much in evidence."

Fig. 2 In ten weeks "the ulcer niche was no longer in evidence roentgenologically or gastroscopically."

Clinical Evaluation of Pro-Banthine®

The case report described below offers significant evidence of the high potency in low dosage of the new, well-tolerated anticholinergic agent, Pro-Banthine.

"M. D., female, aged 48, had a posterior gastrojejunostomy 14 years ago for duodenal ulcer. The patient was fairly well until nine months ago when severe, intractable pains occurred. She was hospitalized and a subtotal gastrectomy was done.

"She remained well for only a few months and was referred to us because of recurrence of very severe pain and marked weight loss. Roentgen study revealed a fairly large ulcer niche on the gastric side of the anastomosis.

"The patient had been on various types of antacids and sedatives without relief from pain. She was given 60 mg. of Pro-Banthine q.i.d. and within 72 hours was able to sleep through the night for the first time in weeks.

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"Ten weeks of controlled regulation was necessary before we were satisfied that the ulcer niche was no longer in evidence roentgenologically or gastroscopically (*Fig. 2*).

"She has been maintained on 30 mg. [q. i. d.] of Pro-Banthine for almost five months with no recurrence of symptoms."[1]

Pro-Banthine (*brand of propantheline bromide*), the new, improved anticholinergic agent, is more potent and, consequently, a smaller dosage is required and side effects are greatly reduced or absent. It is available in 15 mg. tablets as well as in tablets (15 mg.) with Phenobarbital (15 mg.) and in 30 mg. ampuls.

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1. Schwartz, I. R.: Personal communication, Feb. 9, 1953.

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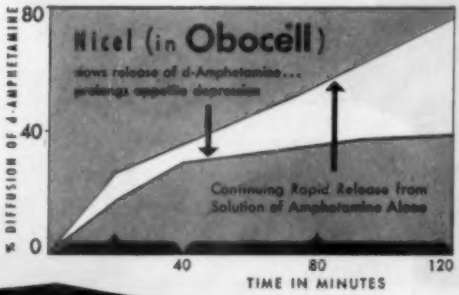

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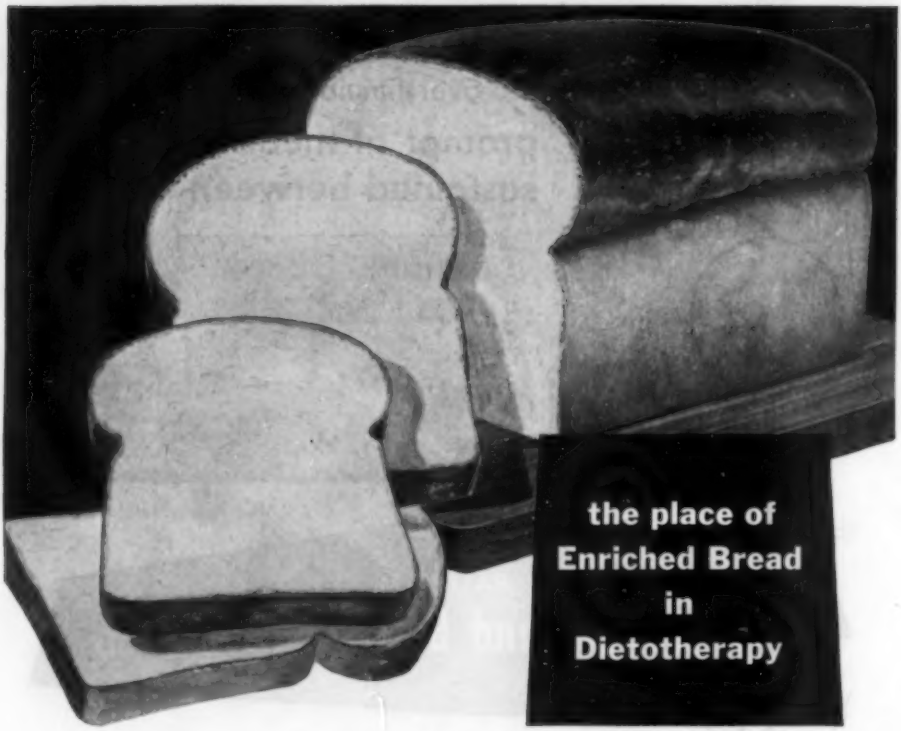

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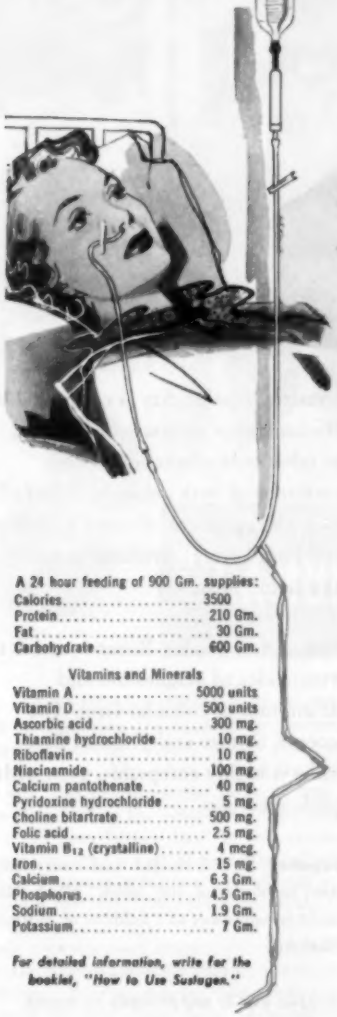

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Calories	3500
Protein	210 Gm.
Fat	30 Gm.
Carbohydrate	600 Gm.

Vitamins and Minerals

Vitamin A	5000 units
Vitamin D	500 units
Ascorbic acid	300 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Calcium pantothenate	40 mg.
Pyridoxine hydrochloride	5 mg.
Choline bitartrate	500 mg.
Folic acid	2.5 mg.
Vitamin B_{12} (crystalline)	4 mcg.
Iron	15 mg.
Calcium	6.3 Gm.
Phosphorus	4.5 Gm.
Sodium	1.9 Gm.
Potassium	7 Gm.

For detailed information, write for the booklet, "How to Use Sustagen."

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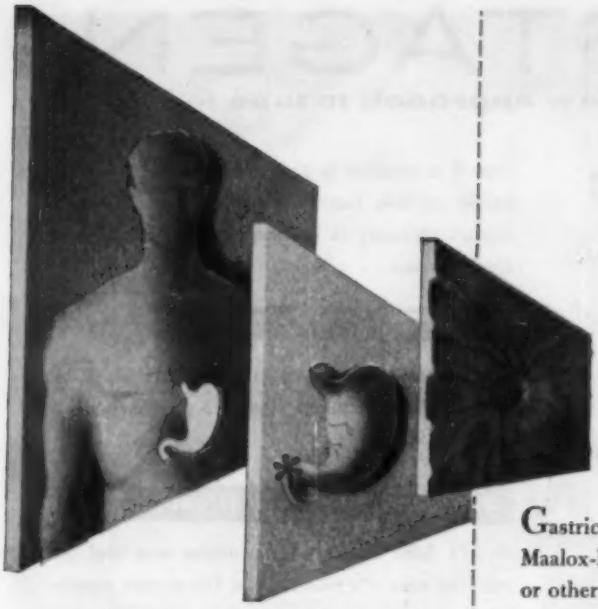

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Parsidol is the substituted phenothiazine diethylamino-propyl-N-dibenzo-parathiazine hydrochloride, with the dynamic parasympathicolytic, antihistaminic, antiacetylcholinic, antinicotinic and antiadrenergic activities indicated in the treatment of the neuromuscular pathology present in parkinsonism.

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Orally administered Parsidol is effective in modifying or abolishing symptoms of parkinsonism such as akinesia, tremor, spasm, festination, sialorrhea, oculogyric crises, and extrapyramidal hypertonicity. This effectiveness, while dependent upon the individual case and necessary dosage regulation, is often superior to that of comparable agents. In addition, Parsidol has produced particularly noteworthy responses when administered in conjunction with other drugs. The value of such combined therapy lies in the enhancement of Parsidol's effect on a specific symptom and in controlling the few side effects of the drug.

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References:

Timberlake, W. H., and Schwab, R. S.: New England J. Med. *247*:98 (July 17) 1952.

Gallagher, D. J. A., and Palmer, H.: New Zealand M. J. *49*:531 (Oct.) 1950.

Reuse, J.: Compt. rend. Soc. de biol. *144*:11563 (July 15) 1950.

Sigwald, J.: Presse méd. *59*:819 (Sept. 17) 1949.

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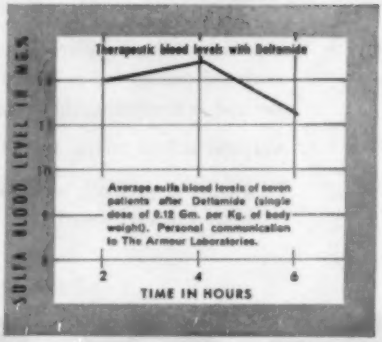
Therapeutic blood levels with Deltamide
Average sulfa blood levels of seven patients after Deltamide (single dose of 0.12 Gm. per Kg. of body weight). Personal communication to The Armour Laboratories.
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TIME IN HOURS
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4
6

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Each tablet, or each teaspoonful (5 cc.), provides:

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Sulfamethazine	0.056 Gm.
Sulfacetamide	0.111 Gm.
Potassium Penicillin G (Buffered)	250,000 units

Tablets: Bottles of 36 and 100.

Powder for Suspension: 60 cc. bottles to provide 2 oz. of suspension by the addition of 40 cc. of water. Deltamide and Deltamide w/Penicillin Suspensions are preferred because of extreme palatability.

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the new fourth dimension in sulfa therapy

Each tablet, or each teaspoonful (5 cc.) of pleasant, chocolate-flavored suspension, provides:

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Sulfamerazine	0.167 Gm.	Sulfacetamide	0.111 Gm.

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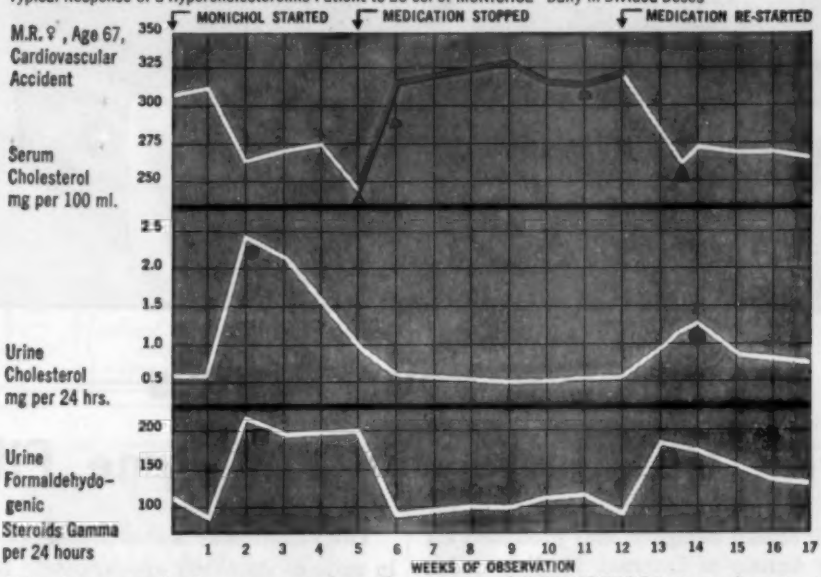

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The sense of well-being experienced by patients on MONICHOL is attributed by the investigators** to better utilization of excess serum cholesterol by the adrenal cortex. MONICHOL is entirely non-toxic.

The red portion of the graph shows that uninterrupted daily intake of MONICHOL is essential, because hypercholesteremia is probably due to an inborn error of metabolism.

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Formula: Each teaspoonful (5 cc.) contains:	
Polysorbate 80	500 mg.
Choline Dihydrogen Citrate	500 mg.
Inositol	250 mg.

Minimum Dosage: Two teaspoonsful twice daily after meals.

Supplied: Bottles of 12 oz.

Literature on request

**Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953. *Trademark

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Bottles of 100
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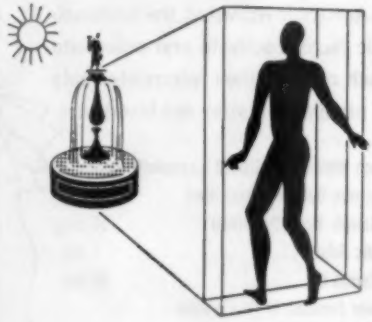

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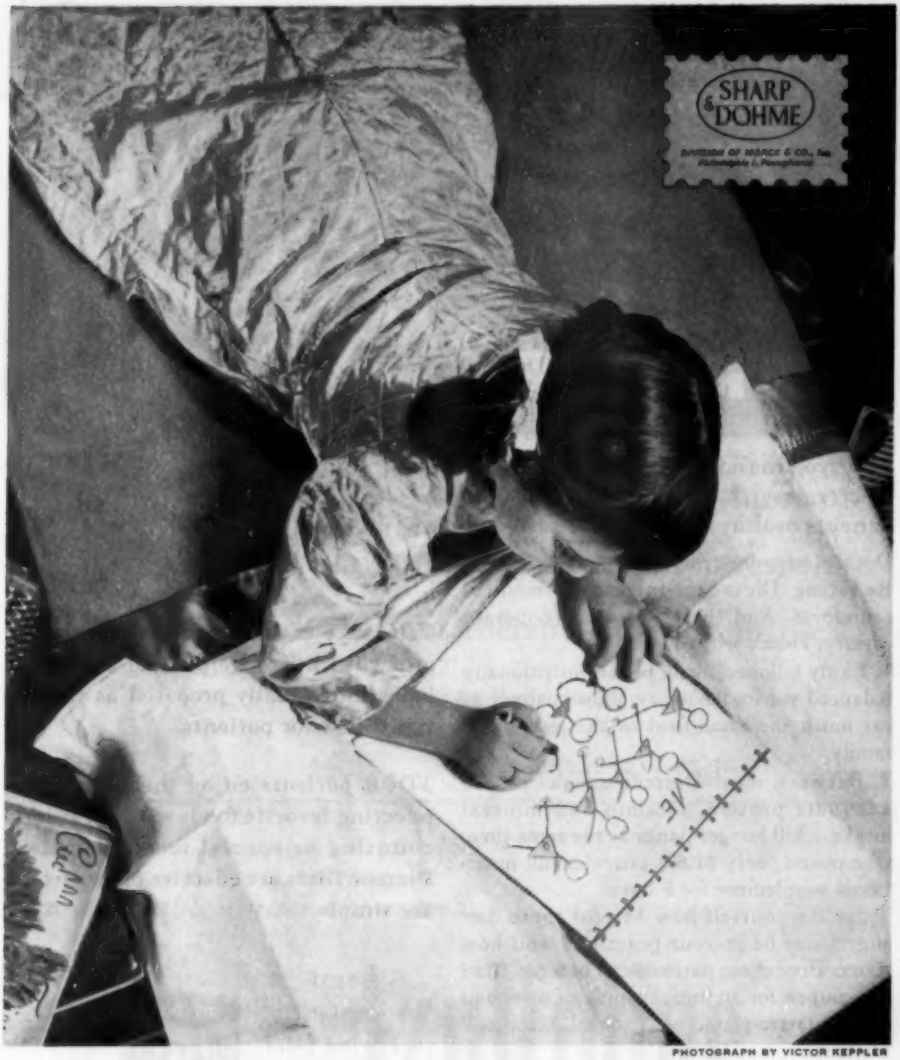

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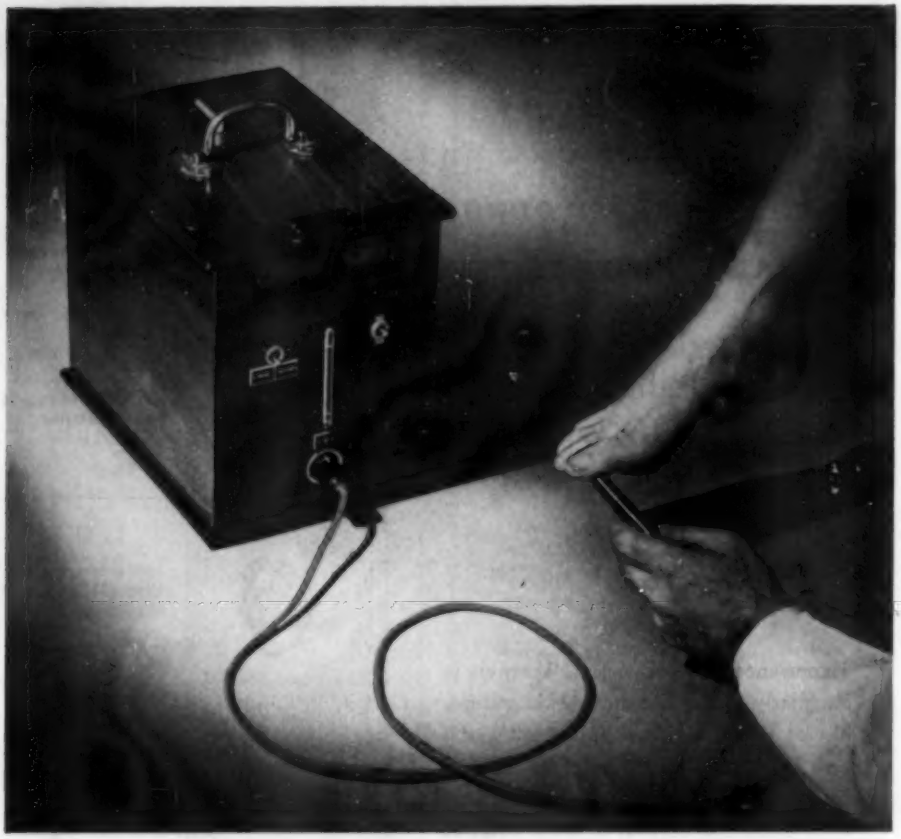

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